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(71) Applicant: **IMMUNOVIA AB** [SE/SE]; Medicon Village, SE-223 81 Lund (SE).

(72) Inventors: **BORREBAECK, Carl**; Helgonavägen 21, SE-223 63 Lund (SE). **DELFANI, Payam**; Ellstorpsgatan 3D, Lgh. 1301, SE-212 17 Malmö (SE). **MELLBY, Linda Dexlin**; Domaregatan 2, SE-247 53 Dalby (SE). **WINGREN, Christer**; Öståkravägen 23, SE-247 32 Södra Sandby (SE).

(74) Agent: **SMITH, Stephen Edward**; Potter Clarkson LLP, The Belgrave Centre, Talbot Street, Nottingham NG1 5GG (GB).

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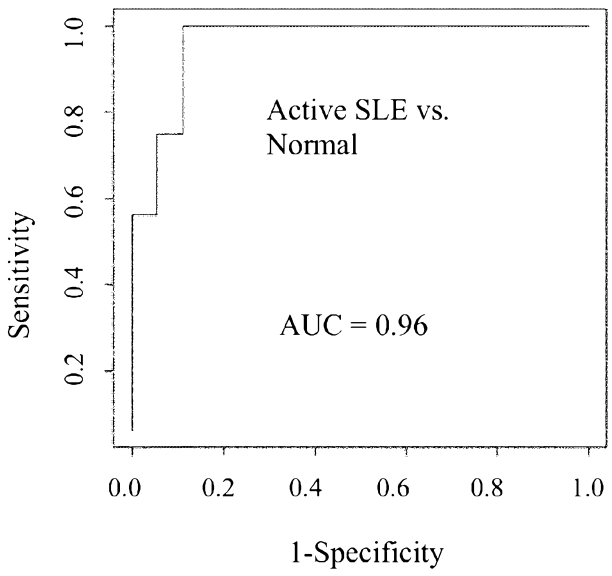
(54) Title: BIOMARKER SIGNATURES OF SYSTEMIC LUPUS ERYTHEMATOSUS AND USES THEREOF

Figure 1(B)



(57) Abstract: The invention provides a method for determining a systemic lupus erythematosus-associated disease state in a subject comprising the steps of (a) providing a sample to be tested; and (b) measuring the presence and/or amount in the test sample of one or more biomarker(s) selected from the group defined in Table A, wherein the presence and/or amount in the test sample of the one or more biomarker(s) selected from the group defined in Table A is indicative of a systemic Lupus-associated disease state. The invention also provides an array and a kit suitable for use in the methods of the invention.

[Continued on next page]

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BIOMARKER SIGNATURES OF SYSTEMIC LUPUS ERYTHEMATOSUS AND USES THEREOF

Field of Invention

The present invention relates to biomarkers for determining a systemic lupus erythematosus-associated disease state, as well as signatures and arrays thereof and methods for use of the same.

Background of the invention

Systemic lupus erythematosus (SLE) is a severe, chronic systemic autoimmune disease with heterogeneous presentation (1, 2). The disease is characterized by alternating periods of flares and remission in a yet unpredictable manner. The treatment of SLE is so far restricted to dealing with the symptoms, essentially trying to reduce and minimize the effects of the flares (3). Accumulation of damage is a function of disease activity over time, side-effects of treatment and/or comorbid conditions, and is linked to morbidity and mortality. Hence, novel means to predict, detect, and monitor the onset, severity, and response of flares, especially to the level of renal activity, would thus be essential to therapeutic regime choice and treatment modifications, as well as prognosis (2-4). Currently, disease activity is assessed using indices, such as SLEDAI-2K, which is based on 24 descriptors in 9 organs (studied over 10 or 30 days) (5). Monitoring of the renal involvement in SLE is often dependent on microscopic evaluation of urine, which has been shown to be associated with large methodological shortcomings (6). So far, renal biopsy has been the gold standard for assessing disease activity and renal involvement, but the need for rapid, minimally invasive methods, such as blood-based tests, is evident.

Historically, mainly single serological biomarkers, such as C1q, C3, C4, IL-6, TNF-α, and various autoantibodies, have been explored for detecting and monitoring flares, but the performance has varied and is generally low (4, 7-11). In more recent years, attempts have therefore been made to decipher panels of biomarkers, better reflecting SLE and SLE disease activity (12-17). As for example, Li and colleagues used 30-plex antigen arrays to delineate candidate serum autoantibody clusters that attempted to distinguish lupus

patients with more severe disease activity (18). Further, Bauer and colleagues pre-validated a 3-plex panel of serum chemokines (IP-10, MCP-1, and MIP3B) for disease activity using conventional antibody microarrays (16, 17).

More recently, high-performing recombinant antibody micro- and nano-array set-ups have been used for deciphering multiplexed serum and urine biomarkers associated with SLE (19, 20) (Nordström *et al*, submitted; Delfani *et al*, 2016, *Lupus* **26**(4):373-387). In those projects, the authors explored the use of the immune system as a specific and sensitive sensor for SLE in an approach denoted clinical immunoproteomics (21) by targeting mainly immunoregulatory proteins. The results showed that multiplexed candidate serum (and urine) biomarkers reflecting SLE, SLE phenotype and SLE disease activity could be deciphered.

However, there remains are continuing need to identify biomarkers and biomarker signatures for disease activity in order to rapidly identify active (flaring) and passive (remissive/non-flaring) disease states to allow quick treatment of flares and withdrawal of therapy during non-flares to minimise the damage caused by non-treatment of the active disease and overtreatment (treatment administration during non-active SLE).

Summary of the invention

The present invention stems from a study of serum protein expression profiling performed using SLE samples collected during flare and remission. A re-optimized recombinant antibody microarray platform, displaying improved performances and targeting a larger set of immunoregulatory proteins (19) (Delfani *et al*, 2016, *supra*) was applied. The results showed that condensed, high-performing serum biomarker signatures reflecting disease activity could be deciphered from crude serum samples.

Accordingly, the first aspect the invention provides a method for determining a systemic lupus erythematosus-associated disease state in a subject measuring the presence and/or amount in a test sample of one or more biomarker selected from the group defined in Table A, wherein the presence and/or amount in the one more test sample of the one or more biomarker(s) selected from the group defined in Table A is indicative of a systemic lupus erythematosus-associated disease state.

Alternative or additionally the method comprises or consists of the steps of:

a) providing a sample to be tested; and

b) measuring the presence and/or amount in the test sample of one or more biomarker(s) selected from the group defined in Table A;

wherein the presence and/or amount in the test sample of the one or more biomarker(s) selected from the group defined in Table A is indicative of the systemic lupus erythematosus-associated disease state in the subject.

Thus, the invention provides biomarkers and biomarker signatures for determining a systemic lupus erythematosus-associated disease state in a subject.

The term "Systemic lupus erythematosus-associated disease state" may mean or include (i) the presence or absence of SLE (e.*g.*, discriminating active SLE from non-SLE, non-active SLE from non-SLE and/or highly active SLE from non-SLE), and (ii) the activity of SLE (e.g., discriminating active SLE from non-active SLE, and/or discriminating highly-active SLE from non-active SLE).

Thus, in one embodiment, the method is for diagnosing active SLE (*e.g.*, an SLE flare) in a subject.

Preferably, the individual is a human, but may be any mammal such as a domesticated mammal (preferably of agricultural or commercial significance including a horse, pig, cow, sheep, dog and cat).

For the avoidance of doubt, test samples from more than one disease state may be provided in step (a), for example, ≥2, ≥3, ≥4, ≥5, ≥6 or ≥7 different disease states. Step (a) may provide at least two test samples, for example, ≥3, ≥4, ≥5, ≥6, ≥7, ≥8, ≥9, ≥10, ≥15, ≥20, ≥25, ≥50 or ≥100 test samples. Where multiple test samples are provided, they may be of the same type (e.g., all serum or urine samples) or of different types (e.g., serum and urine samples).

Alternatively or additionally the method further comprises the steps of:

c) providing a control sample from an individual with a different systemic lupus erythematosus-associated disease state to the test subject; and

d) measuring the presence and/or amount in the control sample of the one or more biomarkers measured in step (b);

wherein the systemic lupus erythematosus-associated disease state is identified in the event that the presence and/or amount in the test sample of the one or more biomarkers measured in step (b) is different from the presence and/or amount in the control sample.

For the avoidance of doubt, control samples from more than one disease state may be provided in step (c), for example, ≥2, ≥3, ≥4, ≥5, ≥6 or ≥7 different disease states. Step (c) may provide at least two control samples, for example, ≥3, ≥4, ≥5, ≥6, ≥7, ≥8, ≥9, ≥10, ≥15, ≥20, ≥25, ≥50 or ≥100 control samples. Where multiple control samples are provided, they may be of the same type (e.g., all serum or urine samples) or of different types (e.g., serum and urine samples). Preferably the test samples types and control samples types are matched/corresponding.

By "is different to the presence and/or amount in a control sample" we mean or include the presence and/or amount of the one or more biomarker in the test sample differs from that of the one or more control sample (or to predefined reference values representing the same). Preferably the presence and/or amount in the test sample differs from the presence or amount in the one or more control sample (or mean of the control samples) by at least ±5%, for example, at least ±6%, ±7%, ±8%, ±9%, ±10%, ±11%, ±12%, ±13%, ±14%, ±15%, ±16%, ±17%, ±18%, ±19%, ±20%, ±21%, ±22%, ±23%, ±24%, ±25%, ±26%, ±27%, ±28%, ±29%, ±30%, ±31%, ±32%, ±33%, ±34%, ±35%, ±36%, ±37%, ±38%, ±39%, ±40%, ±41%, ±42%, ±43%, ±44%, ±45%, ±41%, ±42%, ±43%, ±44%, ±55%, ±60%, ±65%, ±66%, ±67%, ±68%, ±69%, ±70%, ±71%, ±72%, ±73%, ±74%, ±75%, ±76%, ±77%, ±78%, ±79%, ±80%, ±81%, ±82%, ±83%, ±84%, ±85%, ±86%, ±87%, ±88%, ±89%, ±90%, ±91%, ±92%, ±93%, ±94%, ±95%, ±96%, ±97%, ±98%, ±99%, ±100%, ±125%, ±150%, ±175%, ±200%, ±225%, ±250%, ±275%, ±300%, ±350%, ±400%, ±500% or at least ±1000% of the one or more control sample (e.g., the negative control sample).

Alternatively or additionally, the presence or amount in the test sample differs from the mean presence or amount in the control samples by at least >1 standard deviation from the mean presence or amount in the control samples, for example, ≥1.5, ≥2, ≥3, ≥4, ≥5, ≥6, ≥7, ≥8, ≥9, ≥10, ≥11, ≥12, ≥13, ≥14 or ≥15 standard deviations from the from the mean presence or amount in the control samples. Any suitable means may be used for determining standard deviation (e.g., direct, sum of square, Welford's), however, in one embodiment,

standard deviation is determined using the direct method (i.e., the square root of [the sum the squares of the samples minus the mean, divided by the number of samples]).

Alternatively or additionally, by "is different to the presence and/or amount in a control sample" we mean or include that the presence or amount in the test sample does not correlate with the amount in the control sample in a statistically significant manner. By "does not correlate with the amount in the control sample in a statistically significant manner" we mean or include that the presence or amount in the test sample correlates with that of the control sample with a *p*-value of >0.001, for example, >0.002, >0.003, >0.004, >0.005, >0.01, >0.02, >0.03, >0.04 >0.05, >0.06, >0.07, >0.08, >0.09 or >0.1. Any suitable means for determining *p*-value known to the skilled person can be used, including *z*-test, *t*-test, Student's *t*-test, *f*-test, Mann-Whitney *U* test, Wilcoxon signed-rank test and Pearson's chi-squared test.

Alternatively or additionally the method further comprises the steps of:

e) providing a control sample from an individual with the same systemic lupus erythematosus-associated disease state to the test subject; and

f) measuring the presence and/or amount in the control sample of the one or more biomarkers measured in step (b);

wherein the systemic lupus erythematosus-associated disease state is identified in the event that the expression in the test sample of the one or more biomarkers measured in step (b) corresponds to the expression in the control sample of the one or more biomarkers measured in step (f).

For the avoidance of doubt, control samples from more than one disease state may be provided in step (e), for example, ≥2, ≥3, ≥4, ≥5, ≥6 or ≥7 different disease states. Step (e) may provide at least two control samples, for example, ≥3, ≥4, ≥5, ≥6, ≥7, ≥8, ≥9, ≥10, ≥15, ≥20, ≥25, ≥50 or ≥100 control samples. Where multiple control samples are provided, they may be of the same type (e.g., all serum or urine samples) or of different types (e.g., serum and urine samples). Preferably the test samples types and control samples types are matched/corresponding.

By "corresponds to the presence and/or amount in a control sample" we mean or include the presence and/or amount is identical to that of a positive control sample; or closer to that of one or more positive control sample than to one or more negative control sample (or to

predefined reference values representing the same). Preferably the presence and/or amount is within ±40% of that of the one or more control sample (or mean of the control samples), for example, within ±39%, ±38%, ±37%, ±36%, ±35%, ±34%, ±33%, ±32%, ±31%, ±30%, ±29%, ±28%, ±27%, ±26%, ±25%, ±24%, ±23%, ±22%, ±21%, ±20%, ±19%, ±18%, ±17%, ±16%, ±15%, ±14%, ±13%, ±12%, ±11%, ±10%, ±9%, ±8%, ±7%, ±6%, ±5%, ±4%, ±3%, ±2%, ±1%, ±0.05% or within 0% of the one or more control sample (e.g., the positive control sample).

Alternatively or additionally, the difference in the presence or amount in the test sample is ≤5 standard deviation from the mean presence or amount in the control samples, for example, ≤4.5, ≤4, ≤3.5, ≤3, ≤2.5, ≤2, ≤1.5, ≤1.4, ≤1.3, ≤1.2, ≤1.1, ≤1, ≤0.9, ≤0.8, ≤0.7, ≤0.6, ≤0.5, ≤0.4, ≤0.3, ≤0.2, ≤0.1 or 0 standard deviations from the from the mean presence or amount in the control samples, provided that the standard deviation ranges for differing and corresponding biomarker expressions do not overlap (e.g., abut, but no not overlap).

Alternatively or additionally, by "corresponds to the presence and/or amount in a control sample" we mean or include that the presence or amount in the test sample correlates with the amount in the control sample in a statistically significant manner. By "correlates with the amount in the control sample in a statistically significant manner" we mean or include that the presence or amount in the test sample correlates with the that of the control sample with a *p*-value of ≤0.05, for example, ≤0.04, ≤0.03, ≤0.02, ≤0.01, ≤0.005, ≤0.004, ≤0.003, ≤0.002, ≤0.001, ≤0.0005 or ≤0.0001.

Differential expression (up-regulation or down regulation) of biomarkers, or lack thereof, can be determined by any suitable means known to a skilled person. Differential expression is determined to a p value of a least less than 0.05 ($p = < 0.05$), for example, at least <0.04, <0.03, <0.02, <0.01, <0.009, <0.005, <0.001, <0.0001, <0.00001 or at least <0.000001. Alternatively or additionally, differential expression is determined using a support vector machine (SVM). Alternatively or additionally, the SVM is an SVM as described below.

It will be appreciated by persons skilled in the art that differential expression may relate to a single biomarker or to multiple biomarkers considered in combination (i.e. as a biomarker signature). Thus, a p value may be associated with a single biomarker or with a group of biomarkers. Indeed, proteins having a differential expression p value of greater than 0.05 when considered individually may nevertheless still be useful as biomarkers in accordance with the invention when their expression levels are considered in combination with one or more other biomarkers.

As exemplified in the accompanying examples, the expression of certain biomarkers in a tissue, blood, serum or plasma test sample may be indicative of an SLE-associated disease state in an individual. For example, the relative expression of certain serum proteins in a single test sample may be indicative of the activity of SLE in an individual.

In an alternative or additional embodiment, the presence and/or amount in the test sample of the one or more biomarkers measured in step (b) are compared against predetermined reference values representative of the measurements in steps (d) and/or (f).

Alternatively or additionally, step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table A, for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68 or 69 of the biomarkers defined in Table A.

Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of CHX10 (3); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of LUM; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Cyst. C; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of ATP5B (2); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Beta-galactosidase; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of DUSP9; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-1 alpha; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-1 beta; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Motif (13); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Motif (14); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Motif (3); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Motif (4); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Motif (5); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Motif (7); Alternatively

or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Motif (8); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of MYOM2 (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of PSA; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Sox11a; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Surface Ag X; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of TBC1D9 (2); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Angiomotin (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of APOA1 (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of BTK (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of C1 est. inh. (3); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of C1q; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of C1s; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of C3; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of C4; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of C5 (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of CD40; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of CD40 ligand; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Eotaxin (3); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Factor B; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of GLP-1; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of GM-CSF; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of HLA-DR/DP; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of ICAM-1; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IFN-gamma (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IgM; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-10 (1); Alternatively or

additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-11 (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-12 (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-13 (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-16 (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-18; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-1ra; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-2 (2); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-3; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-4; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-5; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-6; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-7; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-8; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of IL-9; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Integrin alpha-10; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of JAK3; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of LDL (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Leptin; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Lewis x (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of MCP-1; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of MCP-3 (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of MCP-4 (2); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Procathepsin W; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of RANTES; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of Sialle x; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of TGF-beta1; Alternatively or additionally, step (b) comprises, consists of or

excludes measuring the presence and/or amount of TNF-alpha (1); Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of TNF-beta; Alternatively or additionally, step (b) comprises, consists of or excludes measuring the presence and/or amount of VEGF (1).

In one embodiment, the biomarker mRNA and/or amino acid sequences correspond to those available on the GenBank database (http://www.ncbi.nlm.nih.gov/genbank/) and natural variants thereof. In a further embodiment, the biomarker mRNA and/or amino acid sequences correspond to those available on the GenBank database on 7 June 2016.

Alternatively or additionally, the method excludes the use of biomarkers that are not listed in Table A and/or the present Examples section.

Alternatively or additionally step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table A(I) and/or (II), for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 of the biomarkers defined in Table A(I) and/or (II).

Alternatively or additionally step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table A(III), for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 21, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48 or 49 of the biomarkers defined in Table A(III).

Alternatively or additionally step (b) comprises or consists of:

a) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(I), for example, 2 or 3 of the biomarkers defined in Table B(I);

b) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(II), for example, 2 or 3 of the biomarkers defined in Table B(II);

c) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(III), for example, 2 of the biomarkers defined in Table B(III);

d) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(IV), for example, 2 of the biomarkers defined in Table B(IV);

e) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(V), for example, 2, 3 or 4 of the biomarkers defined in Table B(V);

f) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(VI), for example, 2 of the biomarkers defined in Table BV(VI);

g) measuring the presence and/or amount in the test sample the biomarker defined in Table B(VII);

h) measuring the presence and/or amount in the test sample the biomarker defined in Table B(VIII);

i) measuring the presence and/or amount in the test sample the biomarker defined in Table B(IX);

j) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(X), for example, 2, 3, 4, 5, 6 or 7 of the biomarkers defined in Table B(X);

k) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(XI), for example, 2, 3, 4, 5, 6, 7 or 8 of the biomarkers defined in Table B(XI);

l) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(XII), for example, 2 or 3 of the biomarkers defined in Table B(XII);

m) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(XIII), for example, 2 of the biomarkers defined in Table B(XIII);

n) measuring the presence and/or amount in the test sample the biomarker defined in Table B(XIV);

o) measuring the presence and/or amount in the test sample the biomarker defined in Table B(XV);

p) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(XVI), for example, 2, 3, 4, 5, 6, 7 or 8 of the biomarkers defined in Table B(XVI);

q) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(XVII), for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 of the biomarkers defined in Table B(XVII);

r) measuring the presence and/or amount in the test sample the biomarker defined in Table B(XVIII); and/or

s) measuring the presence and/or amount in the test sample the biomarker defined in Table B(XIX).

Alternatively or additionally the method comprises, consists of, or is for determining whether the SLE-associated-disease state is active SLE or non SLE. Alternatively or additionally step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(I), (II), (III), (IV), (V), (VI), (VIII), (IX), (X), (XI), (XIV) and/or (XVI).

Alternatively or additionally the method comprises, consists of, or is for determining whether the SLE-associated-disease state is non-active SLE or non SLE. Alternatively or additionally step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(I), (II), (III), (V), (VII), (IX), (X), (XII) and/or (XV).

Alternatively or additionally the method comprises, consists of, or is for determining whether the SLE-associated-disease state is highly active SLE or non SLE. Alternatively or additionally step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(I), (II), (IV), (VI), (XII), (XIII), (XIV) and/or (XVIII).

Alternatively or additionally the method comprises, consists of, or is for determining whether the SLE-associated-disease state is active SLE or non-active SLE. Alternatively or additionally step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(I), (II), (III), (IV), (V), (VII), (VIII), (XI), (XV) and/or (XVII).

Alternatively or additionally the method comprises, consists of, or is for determining whether the SLE-associated-disease state is highly active SLE or non-active SLE. Alternatively or additionally step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(I), (II), (IV), (VI), (XII), (XIII), (XIV) and/or (XVIII).

Alternatively or additionally the method comprises or consists of measuring all the biomarkers listed in Table A and Table B.

Alternatively or additionally the control sample of step (c) or step (e) is provided from:

a) a healthy individual (non-SLE);
b) an individual with non-active SLE (non-flaring SLE);
c) an individual with active SLE (flaring SLE); or
d) an individual with highly-active SLE (strongly flaring SLE).

The healthy individual may be free from SLE, autoimmune disease and/or renal disease. The healthy individual may be free from any form of disease.

By "non-active" we mean or include SLE with a SLEDAI 2000 of less than five. By "active" we mean or include SLE with a SLEDAI 2000 of five to fifteen (i.e., between five and fifteen). By "high active" or "highly active" SLE we mean or include SLE with a SLEDAI 2000 of sixteen or greater.

SLE disease severity and progression are conventionally determined through a clinical assessment and scoring using the following (SLEDAI-2000) criteria (see Gladman *et al.*, 2002; *J. Rheumatol.*, 29(2):288-91):

Wt	Descriptor	Definition
8	Seizure	Recent onset. Exclude metabolic, infectious or drug cause.
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behaviour. Excluded uraemia and drug causes.
8	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intelligent function, with rapid onset fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	Visual Disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serious exodate or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	Lupus Headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.
8	CVA	New onset of cerebrovascular accident(s). Exclude

		arteriosclerosis.
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual, infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	Arthritis	More than 2 joints with pain and signs of inflammation (i.e. tenderness, swelling, or effusion).
4	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/adolase or electromyogram changes or a biopsy showing myositis.
4	Urinary Casts	Heme-granular or red blood cell casts.
4	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	Proteinuria	>0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.
4	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	Rash	Inflammatory type rash.
2	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	Mucosal Ulcers	Oral or nasal ulcerations.
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	Pericarditis	Pericardial pain with at least one of the following: rub, effusion, or electrocardiogram confirmation.
2	Low Complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	Increased DNA binding	>25% binding by Fan assay or above normal range for testing laboratory.
1	Fever	>38°C. Exclude infectious cause
1	Thrombocytopenia	< 100,000 platelets/x10^9/L. Exclude drug causes.
1	Leukopenia	<3,000 White blood cell/x10^9/L. Exclude drug causes.

The corresponding score/weight is applied if a descriptor is present at the time of visit or in the proceeding 10 to 30 days. The score is then totalled. A skilled person will appreciate that the SLEDAI boundaries of passive (remissive) SLE and active (flaring) SLE may vary according to the patient group being assessed.

Alternatively or additionally the lower range for passive (remissive) SLE may be any one of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20; the upper range for passive (remissive) SLE may be any one of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44 or 45; the lower range for active or high active (flaring) SLE may be any one of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20; the upper range for mid severity SLE may be any one of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51,

52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85; the upper range for active or high active (flaring) SLE may be any one of 15, 16, 17, 18, 19 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 105 or 105; with the provisos that the lower range of a particular severity level must be of a lower score than its higher range and the ranges of each severity level may not overlap.

Alternatively or additionally, an increase in SLEDAI score of >3 from the previous assessment indicates mild or moderate flare. An increase in SLEDAI score of >12 from the previous assessment indicates severe flare. A decrease in SLEDAI score of >3 from the previous assessment indicates mild or moderate remission. A decrease in SLEDAI score of >12 from the previous assessment indicates advanced remission. An increase or decrease in SLEDAI score of ≤3 indicates stable (neither flaring nor non-flaring) SLE.

Alternatively or additionally the test sample of step (a) and/or the control sample of step (c) or step (e) is/are individually provided from:

a) an individual with SLE subtype 1 (SLE1);
b) an individual with SLE subtype 2 (SLE2); or
c) an individual with SLE subtype 3 (SLE3).

SLE1 comprises skin and musculoskeletal involvement but lacks serositis, systemic vasculitis and kidney involvement. SLE2 comprises skin and musculoskeletal involvement, serositis and systemic vasculitis but lacks kidney involvement. SLE3 comprises skin and musculoskeletal involvement, serositis, systemic vasculitis and SLE glomerulonephritis. SLE1, SLE2 and SLE3 represent mild/absent, moderate and severe SLE disease states, respectively (e.g., see Sturfelt G, Sjöholm AG. Complement components, complement activation, and acute phase response in systemic lupus erythematosus. Int Arch Allergy Appl Immunol 1984;75:75–83 which is incorporated herein by reference).

Alternatively or additionally the physical symptoms of the SLE-associated disease state are present, for example, for differentiating between active and highly active SLE, the descriptors used to categorise an individual as 'active' or 'highly active' according to SLEDAI 2000 are present. In other words, the method of the invention may be diagnostic of an/the SLE-associated disease state.

By "diagnosing" we mean determining whether a subject is suffering from SLE. Conventional methods of diagnosing SLE are well known in the art.

The American College of Rheumatology established eleven criteria in 1982 (see Tan *et al.*, 1982, The 1982 revised criteria for the classification of systemic lupus erythematosus, *Arthritis. Rheum.*, 25:1271-7), which were revised in 1997 as a classificatory instrument to operationalise the definition of SLE in clinical trials (see Hochberg, 1997, Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, *Arthritis. Rheum.*, 40:1725). For the purpose of identifying patients for clinical studies, a person is taken to have SLE if any 4 out of 11 symptoms are present simultaneously or serially on two separate occasions.

Criterion	**Definition**
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion *OR* Pericarditis--documented by electrocardigram or rub or evidence of pericardial effusion
7. Renal Disorder	Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed OR Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed

8. Neurologic Disorder	Seizures in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance *OR* Psychosis in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	Hemolytic anemia--with reticulocytosis *OR* Leukopenia--< 4,000/mm3 on ≥ 2 occasions *OR* Lyphopenia--< 1,500/ mm3 on ≥ 2 occasions *OR* Thrombocytopenia--<100,000/ mm3 in the absence of offending drugs
10. Immunologic Disorder	Anti-DNA: antibody to native DNA in abnormal titer *OR* Anti-Sm: presence of antibody to Sm nuclear antigen *OR* Positive finding of antiphospholipid antibodies on: (a) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (b) a positive test result for lupus anticoagulant using a standard method, or (c) a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Some people, especially those with antiphospholipid syndrome, may have SLE without four of the above criteria, and also SLE may present with features other than those listed in the

criteria (see Asherson *et al.*, 2003, Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines, *Lupus*, 12(7):530–4; Sangle *et al.*, 2005, Livedo reticularis and pregnancy morbidity in patients negative for antiphospholipid antibodies, *Ann. Rheum. Dis.*, 64(1):147–8; and Hughes and Khamashta, 2003, Seronegative antiphospholipid syndrome, *Ann. Rheum. Dis.*, 62(12):1127).

Recursive partitioning has been used to identify more parsimonious criteria (see Edworthy *et al.*, 1988, Analysis of the 1982 ARA lupus criteria data set by recursive partitioning methodology: new insights into the relative merit of individual criteria, *J. Rheumatol.*, 15(10):1493–8). This analysis presented two diagnostic classification trees:

Simplest classification tree: SLE is diagnosed if a person has an immunologic disorder (anti-DNA antibody, anti-Smith antibody, false positive syphilis test, or LE cells) or malar rash.

Full classification tree: Uses 6 criteria.

Alternatively or additionally, the diagnosis of SLE in is made according to the principles outlined by Fries and Holman, in: Smith LH Jr, ed. In: Smith LH Jr, ed. major Problems in Internal Medicine. Vol VI., 1976, which is incorporated herein by reference.

Other alternative set of criteria has been suggested, the St. Thomas' Hospital "alternative" criteria in 1998 (see Hughes, 1998, Is it lupus? The St. Thomas' Hospital "alternative" criteria, *Clin. Exp. Rheumatol.*, 16(3):250–2).

However, these criteria were not intended to be used to diagnose individuals. They are time-consuming, subjective, require a high degree of experience to use effectively and have a high frequency of excluding actual SLE sufferers (i.e., diagnosing SLE patients as non-SLE patients). The present invention addresses these problems, providing objective SLE diagnosis.

Alternatively or additionally the SLE-associated disease state is determined before the appearance of the physical symptoms of the SLE-associated disease state, for example, for differentiating between active and highly active SLE, the descriptors used to categorise an individual as 'active' or 'highly active' according to SLEDAI 2000 are not yet present. Hence, the individual may be categorised as belonging to a first disease state by the method of the present invention but categorised as a second disease state according to SLEDAI

2000. In other words, the method of the invention may be prognostic of an/the SLE-associated disease state.

Alternatively or additionally, the SLE-associated disease state may be determined at least 1 day before the appearance of the physical symptoms of the SLE associated disease state, for example, at least 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, five f months or, six 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 13 months, 14, months, 15, months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months or 24 months before the appearance of the physical symptoms of the SLE-associated disease state.

By "expression" we include the level or amount of a gene product such as mRNA or protein.

By 'Motif #' (wherein '#' represents a number) we include a protein comprising the selection motif shown in Table B. Alternatively or additionally we include a protein specifically bound by an antibody having the CDRs defined in Table B in respect of the motif in question. Alternatively or additionally the antibody has a framework region as defined in Olsson et al., 2012, 'Epitope-specificity of recombinant antibodies reveals promiscuous peptide-binding properties.' Protein Sci., 21(12):1897-910.

Generally, the systemic lupus erythematosus-associated disease state in a subject is determined with an ROC AUC of at least 0.55, for example with an ROC AUC of at least, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 0.96, 0.97, 0.98 or with an ROC AUC of at least 0.99. Preferably, the systemic lupus erythematosus-associated disease state in an individual is determined with an ROC AUC of at least 0.85.

Typically, the systemic lupus erythematosus-associated disease state in a subject is determined using a support vector machine (SVM), such as those available from http://cran.r-project.org/web/packages/e1071/index.html (e.g. e1071 1.5-24). However, any other suitable means may also be used.

Support vector machines (SVMs) are a set of related supervised learning methods used for classification and regression. Given a set of training examples, each marked as belonging to one of two categories, an SVM training algorithm builds a model that predicts whether a new example falls into one category or the other. Intuitively, an SVM model is a

representation of the examples as points in space, mapped so that the examples of the separate categories are divided by a clear gap that is as wide as possible. New examples are then mapped into that same space and predicted to belong to a category based on which side of the gap they fall on.

More formally, a support vector machine constructs a hyperplane or set of hyperplanes in a high or infinite dimensional space, which can be used for classification, regression or other tasks. Intuitively, a good separation is achieved by the hyperplane that has the largest distance to the nearest training datapoints of any class (so-called functional margin), since in general the larger the margin the lower the generalization error of the classifier. For more information on SVMs, see for example, Burges, 1998, *Data Mining and Knowledge Discovery*, **2**:121–167.

In one embodiment of the invention, the SVM is 'trained' prior to performing the methods of the invention using proteome samples from subjects assigned to known patient groups (namely, those patients in which the systemic lupus erythematosus-associated disease state is present versus those patients in which it is absent). By running such training samples, the SVM is able to learn what biomarker profiles are associated with the systemic lupus erythematosus-associated disease state. Once the training process is complete, the SVM is then able whether or not the proteome sample tested is from a subject a systemic lupus erythematosus-associated disease state.

However, this training procedure can be by-passed by pre-programming the SVM with the necessary training parameters. For example, a systemic lupus erythematosus-associated disease state in a subject can be determined using the SVM parameters detailed in Table B, based on the measurement of some or all the biomarkers listed in Table A.

It will be appreciated by skilled persons that suitable SVM parameters can be determined for any combination of the biomarkers listed Table A by training an SVM machine with the appropriate selection of data (i.e. biomarker measurements in samples from known patient groups.

Alternatively, the data provided in the present figures and tables may be used to determine a particular SLE-associated disease state according to any other suitable statistical method known in the art, such as Principal Component Analysis (PCA) Orthogonal PCA (OPLS) and other multivariate statistical analyses (e.g., backward stepwise logistic regression model). For a review of multivariate statistical analysis see, for example, Schervish, Mark

J. (November 1987). "A Review of Multivariate Analysis". *Statistical Science* **2** (4): 396–413 which is incorporated herein by reference.

Preferably, the method of the invention has an accuracy of at least 51%, for example 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% accuracy.

Preferably, the method of the invention has a sensitivity of at least 51%, for example 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sensitivity.

Preferably, the method of the invention has a specificity of at least 51%, for example 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% specificity.

By “accuracy” we mean the proportion of correct outcomes of a method, by “sensitivity” we mean the proportion of all positive chemicals that are correctly classified as positives, and by “specificity” we mean the proportion of all negative chemicals that are correctly classified as negatives.

Alternatively or additionally step (b) and/or step (d) is performed using a binding agent capable of binding to the one or more biomarker(s). Binding agents (also referred to as binding molecules and binding moieties) can be selected from a library, based on their ability to bind a given motif, as discussed below.

By “biomarker” we mean a naturally-occurring biological molecule, or component or fragment thereof, the measurement of which can provide information useful in the prognosis of pancreatic cancer. For example, the biomarker may be a naturally occurring protein, mRNA or carbohydrate moiety, or an antigenic component or fragment thereof.

In an alternative or additional embodiment step (b) comprises measuring the expression of the protein or polypeptide of the one or more biomarker(s).

Methods of detecting and/or measuring the concentration of protein and/or nucleic acid are well known to those skilled in the art, see for example Sambrook and Russell, 2001, Cold Spring Harbor Laboratory Press.

Preferred methods for detection and/or measurement of protein include Western blot, North-Western blot, immunosorbent assays (ELISA), antibody microarray, tissue microarray (TMA), immunoprecipitation, *in situ* hybridisation and other immunohistochemistry techniques, radioimmunoassay (RIA), immunoradiometric assays (IRMA) and immunoenzymatic assays (IEMA), including sandwich assays using monoclonal and/or polyclonal antibodies. Exemplary sandwich assays are described by David *et al.*, in US Patent Nos. 4,376,110 and 4,486,530, hereby incorporated by reference. Antibody staining of cells on slides may be used in methods well known in cytology laboratory diagnostic tests, as well known to those skilled in the art.

Typically, ELISA involves the use of enzymes which give a coloured reaction product, usually in solid phase assays. Enzymes such as horseradish peroxidase and phosphatase have been widely employed. A way of amplifying the phosphatase reaction is to use NADP as a substrate to generate NAD which now acts as a coenzyme for a second enzyme system. Pyrophosphatase from *Escherichia coli* provides a good conjugate because the enzyme is not present in tissues, is stable and gives a good reaction colour. Chemi-luminescent systems based on enzymes such as luciferase can also be used.

Conjugation with the vitamin biotin is frequently used since this can readily be detected by its reaction with enzyme-linked avidin or streptavidin to which it binds with great specificity and affinity.

Alternatively or additionally, the binding agent is an antibody or a fragment thereof.

Thus, a fragment may contain one or more of the variable heavy (V_H) or variable light (V_L) domains. For example, the term antibody fragment includes Fab-like molecules (Better *et al* (1988) *Science* **240**, 1041); Fv molecules (Skerra *et al* (1988) *Science* **240**, 1038); single-chain Fv (ScFv) molecules where the V_H and V_L partner domains are linked via a flexible oligopeptide (Bird *et al* (1988) *Science* **242**, 423; Huston *et al* (1988) *Proc. Natl. Acad. Sci. USA* **85**, 5879) and single domain antibodies (dAbs) comprising isolated V domains (Ward *et al* (1989) *Nature* **341**, 544).

The term "antibody variant" includes any synthetic antibodies, recombinant antibodies or antibody hybrids, such as but not limited to, a single-chain antibody molecule produced by phage-display of immunoglobulin light and/or heavy chain variable and/or constant regions, or other immunointeractive molecule capable of binding to an antigen in an immunoassay format that is known to those skilled in the art.

A general review of the techniques involved in the synthesis of antibody fragments which retain their specific binding sites is to be found in Winter & Milstein (1991) *Nature* **349**, 293-299.

Additionally or alternatively at least one type, more typically all of the types, of the binding molecules is an aptamer.

Molecular libraries such as antibody libraries (Clackson *et al*, 1991, *Nature* **352**, 624-628; Marks *et al*, 1991, *J Mol Biol* **222**(3): 581-97), peptide libraries (Smith, 1985, *Science* **228**(4705): 1315-7), expressed cDNA libraries (Santi et al (2000) *J Mol Biol* 296(2): 497-508), libraries on other scaffolds than the antibody framework such as affibodies (Gunneriusson *et al*, 1999, *Appl Environ Microbiol* **65**(9): 4134-40) or libraries based on aptamers (Kenan *et al*, 1999, *Methods Mol Biol* **118**, 217-31) may be used as a source from which binding molecules that are specific for a given motif are selected for use in the methods of the invention.

The molecular libraries may be expressed *in vivo* in prokaryotic (Clackson *et al*, 1991, *op. cit.*; Marks *et al*, 1991, *op. cit.*) or eukaryotic cells (Kieke *et al*, 1999, *Proc Natl Acad Sci USA*, **96**(10):5651-6) or may be expressed *in vitro* without involvement of cells (Hanes & Pluckthun, 1997, *Proc Natl Acad Sci USA* **94**(10):4937-42; He & Taussig, 1997, *Nucleic Acids Res* **25**(24):5132-4; Nemoto *et al*, 1997, *FEBS Lett*, **414**(2):405-8).

In cases when protein based libraries are used often the genes encoding the libraries of potential binding molecules are packaged in viruses and the potential binding molecule is displayed at the surface of the virus (Clackson *et al*, 1991, *op. cit.*; Marks *et al*, 1991, *op. cit*; Smith, 1985, *op. cit.*).

The most commonly used such system today is filamentous bacteriophage displaying antibody fragments at their surfaces, the antibody fragments being expressed as a fusion to the minor coat protein of the bacteriophage (Clackson *et al*, 1991, *op. cit.*; Marks *et al*, 1991, *op. cit*). However, also other systems for display using other viruses (EP 39578),

bacteria (Gunneriusson *et al*, 1999, *op. cit.*; Daugherty *et al*, 1998, *Protein Eng* **11**(9):825-32; Daugherty *et al*, 1999, *Protein Eng* **12**(7):613-21), and yeast (Shusta *et al*, 1999, *J Mol Biol* **292**(5):949-56) have been used.

In addition, recently, display systems utilising linkage of the polypeptide product to its encoding mRNA in so called ribosome display systems (Hanes & Pluckthun, 1997, *op. cit.*; He & Taussig, 1997, *op. cit.*; Nemoto *et al*, 1997, *op. cit.*), or alternatively linkage of the polypeptide product to the encoding DNA (see US Patent No. 5,856,090 and WO 98/37186) have been presented.

When potential binding molecules are selected from libraries one or a few selector peptides having defined motifs are usually employed. Amino acid residues that provide structure, decreasing flexibility in the peptide or charged, polar or hydrophobic side chains allowing interaction with the binding molecule may be used in the design of motifs for selector peptides. For example –

(i) Proline may stabilise a peptide structure as its side chain is bound both to the alpha carbon as well as the nitrogen;

(ii) Phenylalanine, tyrosine and tryptophan have aromatic side chains and are highly hydrophobic, whereas leucine and isoleucine have aliphatic side chains and are also hydrophobic;

(iii) Lysine, arginine and histidine have basic side chains and will be positively charged at neutral pH, whereas aspartate and glutamate have acidic side chains and will be negatively charged at neutral pH;

(iv) Asparagine and glutamine are neutral at neutral pH but contain a amide group which may participate in hydrogen bonds;

(v) Serine, threonine and tyrosine side chains contain hydroxyl groups, which may participate in hydrogen bonds.

Typically selection of binding molecules may involve the use of array technologies and systems to analyse binding to spots corresponding to types of binding molecules.

In one embodiment, the antibody or fragment thereof is a recombinant antibody or fragment thereof (such as an scFv).

By "ScFv molecules" we mean molecules wherein the V_H and V_L partner domains are linked via a flexible oligopeptide.

The advantages of using antibody fragments, rather than whole antibodies, are several-fold. The smaller size of the fragments may lead to improved pharmacological properties, such as better penetration of solid tissue. Effector functions of whole antibodies, such as complement binding, are removed. Fab, Fv, ScFv and dAb antibody fragments can all be expressed in and secreted from *E. coli*, thus allowing the facile production of large amounts of the said fragments.

Whole antibodies, and $F(ab')_2$ fragments are "bivalent". By "bivalent" we mean that the said antibodies and $F(ab')_2$ fragments have two antigen combining sites. In contrast, Fab, Fv, ScFv and dAb fragments are monovalent, having only one antigen combining sites.

The antibodies may be monoclonal or polyclonal. Suitable monoclonal antibodies may be prepared by known techniques, for example those disclosed in "Monoclonal Antibodies: A manual of techniques", H Zola (CRC Press, 1988) and in "Monoclonal Hybridoma Antibodies: Techniques and applications", J G R Hurrell (CRC Press, 1982), both of which are incorporated herein by reference.

Alternatively or additionally the antibody or fragment thereof is selected from the group consisting of: scFv; Fab; a binding domain of an immunoglobulin molecule.

Alternatively or additionally, antibody or antigen-binding fragment is capable of competing for binding to a biomarker specified in Table A with an antibody for that biomarker defined in Table C.

By "capable of competing" for binding to a biomarker specified in Table A with an antibody molecule as defined herein (or a variant, fusion or derivative of said antibody or antigen-binding fragment, or a fusion of a said variant or derivative thereof, which retains the binding specificity for the required biomarker) we mean or include that the tested antibody or antigen-binding fragment is capable of inhibiting or otherwise interfering, at least in part, with the binding of an antibody molecule as defined herein.

For example, the antibody or antigen-binding fragment may be capable of inhibiting the binding of an antibody molecule defined herein by at least 10%, for example at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 35% or even by 100%.

Competitive binding may be determined by methods well known to those skilled in the art, such as ELISA (as described herein) and/or SPR (as described in the accompanying Examples).

Alternatively or additionally, the antibody or antigen-binding fragment is an antibody defined in Table C or an antigen-binding fragment thereof, or a variant thereof.

Alternatively or additionally, the antibody the antibody or antigen-binding fragment comprises a VH and VL domain specified in Table C, or a variant thereof.

By 'variants' of the antibody or antigen-binding fragment of the invention we include insertions, deletions and substitutions, either conservative or non-conservative. In particular we include variants of the sequence of the antibody or antigen-binding fragment where such variations do not substantially alter the activity of the antibody or antigen-binding fragment. In particular, we include variants of the antibody or antigen-binding fragment where such changes do not substantially alter the binding specificity for the respective biomarker specified in Table C.

The polypeptide variant may have an amino acid sequence which has at least 70% identity with one or more of the amino acid sequences of the antibody or antigen-binding fragment of the invention as defined herein – for example, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identity with one or more of the amino acid sequences of the antibody or antigen-binding fragment of the invention as defined herein.

The percent sequence identity between two polypeptides may be determined using suitable computer programs, for example the GAP program of the University of Wisconsin Genetic Computing Group and it will be appreciated that percent identity is calculated in relation to polypeptides whose sequences have been aligned optimally.

The alignment may alternatively be carried out using the Clustal W program (as described in Thompson *et al.,* 1994, *Nucl. Acid Res.* **22**:4673-4680, which is incorporated herein by reference).

The parameters used may be as follows:

- Fast pair-wise alignment parameters: K-tuple(word) size; 1, window size; 5, gap penalty; 3, number of top diagonals; 5. Scoring method: x percent.
- Multiple alignment parameters: gap open penalty; 10, gap extension penalty; 0.05.
- Scoring matrix: BLOSUM.

Alternatively, the BESTFIT program may be used to determine local sequence alignments.

The antibodies may share CDRs (e.g., 1, 2, 3, 4, 5 or 6) CDRs with one or more of the antibodies defined in Table C.

CDRs can be defined using any suitable method known in the art. Commonly used methods include Paratome (Kunik, Ashkenazi and Ofran, 2012, 'Paratome: an online tool for systematic identification of antigen-binding regions in antibodies based on sequence or structure' *Nucl. Acids Res.*, 40:W521–W524; http://www.ofranlab.org/paratome/), Kabat (Wu and Kabat, 1970, 'An analysis of the sequences of the variable regions of Bence Jones proteins and myeloma light chains and their implications for antibody complementarity.' *J. Exp. Med.*, 132:211-250), Chothia (Chothia and Lesk, 1987 'Canonical structures for the hypervariable regions of immunoglobulins' *J. Mol. Biol.*, 196:901-917; Chothia et al., 1989 'Conformations of immunoglobulin hypervariable regions' Nature, 342:877-883) and IMGT (Lefranc et al., 2003 'IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains. *Dev. Comp. Immunol.*, 27:55–77; Lefranc et al., 2005 'IMGT unique numbering for immunoglobulin and T cell receptor constant domains and Ig superfamily C-like domains' *Dev. Comp. Immunol.*, 29:185-203; http://www.imgt.org). For example, the method used may be the IMGT method.

Alternatively or additionally, the first binding agent is immobilised on a surface (e.g., on a multiwell plate or array).

Alternatively or additionally the one or more biomarker(s) in the test sample is labelled with a detectable moiety.

Alternatively or additionally the one or more biomarker(s) in the control sample is labelled with a detectable moiety (which may be the same or different from the detectable moiety used to label the test sample).

By a "detectable moiety" we include the meaning that the moiety is one which may be detected and the relative amount and/or location of the moiety (for example, the location on an array) determined.

Detectable moieties are well known in the art.

A detectable moiety may be a fluorescent and/or luminescent and/or chemiluminescent moiety which, when exposed to specific conditions, may be detected. For example, a fluorescent moiety may need to be exposed to radiation (*i.e.* light) at a specific wavelength and intensity to cause excitation of the fluorescent moiety, thereby enabling it to emit detectable fluorescence at a specific wavelength that may be detected.

Alternatively, the detectable moiety may be an enzyme which is capable of converting a (preferably undetectable) substrate into a detectable product that can be visualised and/or detected. Examples of suitable enzymes are discussed in more detail in relation to, for example, ELISA assays.

Alternatively, the detectable moiety may be a radioactive atom which is useful in imaging. Suitable radioactive atoms include ^{99m}Tc and ^{123}I for scintigraphic studies. Other readily detectable moieties include, for example, spin labels for magnetic resonance imaging (MRI) such as ^{123}I again, ^{131}I, ^{111}In, ^{19}F, ^{13}C, ^{15}N, ^{17}O, gadolinium, manganese or iron. Clearly, the agent to be detected (such as, for example, the one or more proteins in the test sample and/or control sample described herein and/or an antibody molecule for use in detecting a selected protein) must have sufficient of the appropriate atomic isotopes in order for the detectable moiety to be readily detectable.

The radio- or other labels may be incorporated into the agents of the invention (i.e. the proteins present in the samples of the methods of the invention and/or the binding agents of the invention) in known ways. For example, if the binding moiety is a polypeptide it may be biosynthesised or may be synthesised by chemical amino acid synthesis using suitable amino acid precursors involving, for example, fluorine-19 in place of hydrogen. Labels such as ^{99m}Tc, ^{123}I, ^{186}Rh, ^{188}Rh and ^{111}In can, for example, be attached *via* cysteine residues in the binding moiety. Yttrium-90 can be attached via a lysine residue. The IODOGEN method (Fraker *et al* (1978) *Biochem. Biophys. Res. Comm.* **80**, 49-57) can be used to incorporate ^{123}I. Reference ("Monoclonal Antibodies in Immunoscintigraphy", J-F Chatal, CRC Press, 1989) describes other methods in detail. Methods for conjugating other detectable moieties

(such as enzymatic, fluorescent, luminescent, chemiluminescent or radioactive moieties) to proteins are well known in the art.

Preferably, the detectable moiety is selected from the group consisting of: a fluorescent moiety, a luminescent moiety, a chemiluminescent moiety, a radioactive moiety, and an enzymatic moiety.

In an alternative or additional embodiment step (b), (d) and/or (f) comprises measuring the expression of a nucleic acid molecule encoding the one or more biomarkers.

The nucleic acid molecule may be a cDNA molecule or an mRNA molecule. Preferably the nucleic acid molecule is an mRNA molecule. Also preferably the nucleic acid molecule is a cDNA molecule.

Hence, measuring the expression of the one or more biomarker(s) in step (b) may be performed using a method selected from the group consisting of Southern hybridisation, Northern hybridisation, polymerase chain reaction (PCR), reverse transcriptase PCR (RT-PCR), quantitative real-time PCR (qRT-PCR), nanoarray, microarray, macroarray, autoradiography and *in situ* hybridisation. Preferably measuring the expression of the one or more biomarker(s) in step (b) is determined using a DNA microarray. Hence, the method may comprise or consist of measuring the expression of the one or more biomarker(s) in step (b) using one or more binding moiety, each capable of binding selectively to a nucleic acid molecule encoding one of the biomarkers identified in Table A.

In an alternative or additional embodiment step the one or more binding moieties each comprise or consist of a nucleic acid molecule such as DNA, RNA, PNA, LNA, GNA, TNA or PMO (preferably DNA). Preferably the one or more binding moieties are 5 to 100 nucleotides in length. More preferably, the one or more nucleic acid molecules are 15 to 35 nucleotides in length. The binding moiety may comprise a detectable moiety.

Suitable binding agents (also referred to as binding molecules) may be selected or screened from a library based on their ability to bind a given nucleic acid, protein or amino acid motif.

In an alternative or additional embodiment measuring the expression of the one or more biomarker(s) in step (b), (d) and/or (f) is performed using one or more binding moieties, each individually capable of binding selectively to a nucleic acid molecule encoding one of the biomarkers identified in Table A.

In an alternative or additional embodiment, the nucleic acid binding moiety comprises a detectable moiety as defined above.

Alternatively or additionally step (b), (d) and/or (f), where present, is performed using an array. The array may be a bead-based array or a surface-based array. The array may be selected from the group consisting of macroarray, microarray and nanoarray.

Arrays *per se* are well known in the art. Typically, they are formed of a linear or two-dimensional structure having spaced apart (*i.e.* discrete) regions ("spots"), each having a finite area, formed on the surface of a solid support. An array can also be a bead structure where each bead can be identified by a molecular code or colour code or identified in a continuous flow. Analysis can also be performed sequentially where the sample is passed over a series of spots each adsorbing the class of molecules from the solution. The solid support is typically glass or a polymer, the most commonly used polymers being cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene. The solid supports may be in the form of tubes, beads, discs, silicon chips, microplates, polyvinylidene difluoride (PVDF) membrane, nitrocellulose membrane, nylon membrane, other porous membrane, non-porous membrane (e.g. plastic, polymer, perspex, silicon, amongst others), a plurality of polymeric pins, or a plurality of microtitre wells, or any other surface suitable for immobilising proteins, polynucleotides and other suitable molecules and/or conducting an immunoassay. The binding processes are well known in the art and generally consist of cross-linking covalently binding or physically adsorbing a protein molecule, polynucleotide or the like to the solid support. By using well-known techniques, such as contact or non-contact printing, masking or photolithography, the location of each spot can be defined. For reviews see Jenkins, R.E., Pennington, S.R. (2001, *Proteomics*, **2**,13-29) and Lal *et al* (2002, *Drug Discov Today* **15**;7(18 Suppl):S143-9).

Typically, the array is a microarray. By "microarray" we include the meaning of an array of regions having a density of discrete regions of at least about 100/cm^2, and preferably at least about 1000/cm^2. The regions in a microarray have typical dimensions, e.g., diameters, in the range of between about 10-250 μm, and are separated from other regions in the array by about the same distance. The array may also be a macroarray or a nanoarray.

Once suitable binding molecules (discussed above) have been identified and isolated, the skilled person can manufacture an array using methods well known in the art of molecular biology.

Alternatively or additionally step (b), step (d) and/or step (f), where present, is performed using an assay comprising a second binding agent capable of binding to the one or more proteins, the second binding agent having a detectable moiety.

Alternatively or additionally step (b), step (d) and/or step (f), where present, are performed using ELISA (Enzyme Linked Immunosorbent Assay).

Typically, the assay is an ELISA (Enzyme Linked Immunosorbent Assay) which typically involve the use of enzymes which give a coloured reaction product, usually in solid phase assays. Enzymes such as horseradish peroxidase and phosphatase have been widely employed. A way of amplifying the phosphatase reaction is to use NADP as a substrate to generate NAD which now acts as a coenzyme for a second enzyme system. Pyrophosphatase from *Escherichia coli* provides a good conjugate because the enzyme is not present in tissues, is stable and gives a good reaction colour. Chemi-luminescent systems based on enzymes such as luciferase can also be used.

Conjugation with the vitamin biotin is also employed used since this can readily be detected by its reaction with enzyme-linked avidin or streptavidin to which it binds with great specificity and affinity.

It will be appreciated by persons skilled in the art that there is a degree of fluidity in the biomarker composition of the signatures of the invention. Thus, different combinations of the biomarkers may be equally useful in the diagnosis, prognosis and/or characterisation of SLE. In this way, each biomarker (either alone or in combination with one or more other biomarkers) makes a contribution to the signature.

Alternatively or additionally step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers listed in Figure 1(E), Figure 2(D), Figure 2(H), Figure 3(D), Figure 3(E), Figure 3(F), Figure 4(A), Figure 5(A), Figure 5(B), Figure 8(A), Figure 8(B), Figure 8(C) and/or Figure 8(D).

In an alternative or additional embodiment the method comprises recording the diagnosis, prognosis or characterisation on a physical or electronic data carrier (i.e., physical or electronic file).

In an alternative or additional embodiment the method comprises the step of:

(g) determining an/the systemic lupus erythematosus-associated disease state in the subject based on the presence and/or amount in the test sample of the one or more biomarker(s) selected from the group defined in Table A.

In an alternative or additional embodiment in the event that the individual is diagnosed with SLE, the method comprises the step of:

(h) providing the individual with appropriate SLE therapy.

In the event that the individual is not diagnosed with SLE, they may be subjected to further monitoring for SLE (for example, using the method of the present invention).

In an alternative or additional embodiment in the event that the individual is characterised or prognosed as having a flare in SLE (i.e., active or highly active SLE), the method comprises the step of:

(h) providing the individual with appropriate SLE flare therapy.

Treatment may be withdrawn, reduced or otherwise modified in individuals being treated for SLE flare where it is found that the individual is not or is no longer experiencing flare. Hence, the patient is provided treatment appropriate to their SLE-associated disease state. In an alternative or additional embodiment, a more aggressive treatment may be provided for more aggressive SLE types (e.g., SLE3) or during an SLE flare. Suitable therapeutic approaches can be determined by the skilled person according to the prevailing guidance at the time, for example, the American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis (Hahn *et al.*, 2012, *Arthritis Care & Research*, 64(6):797–808) which is incorporated herein by reference.

As noted above, in the event that the individual is not diagnosed with SLE flare, they may be subjected to further monitoring for SLE flare (for example, using the method of the present invention).

The repeated monitoring may be repeated at least every 5 days, for example, at least every 10 days, at least every 15 days, at least every 20 days, at least every 25 days, at least every 30 days, at least every 2 months, at least every 3 months, at least every 4 months, at least

every 5 months, at least every 6 months, at least every 7 months, at least every 8 months, at least every 9 months, at least every 10 months, at least every 11 months, at least every 12 months, at least every 18 months or at least every 24 months.

Monitoring may also continue in a repeated fashion regardless of whether or not the individual is found to have SLE or SLE flare.

In an alternative or additional embodiment the SLE therapy is selected from the group consisting of systemic inflammation directed treatment (Antimalarials (Hydroxychloroquine), Corticosteroids, Pulse (or mini-pulse) cyclophosphamide (CTX) (with or without corticosteroid co-administration), Mycophenolate mofetil (MMF), Azathioprine (AZA), Methotrexate (MTX)), immune cell targeted therapies (Anti-CD20 antibodies (rituximab, atumumab, ocrelizumab and veltuzumumab), anti-CD22 (Epratuzumab), abetimus (LJP-394), belimumab, atacicept), co-stimulatory signalling pathway targeting (anti-ICOS (inducible costimulator) antibody, anti-ICOS-L (inducible costimulator ligand) antibody, anti-B7RP1 antibody (AMG557)), anti-cytokine therapy (anti-TNF therapy, anti-IL-10, anti-IL-1, anti-IL-18, anti-IL-6, anti-IL-15, memantine, anti-interferon-alpha (IFN-α), plasmapheresis (or plasma exchange), intravenous immunoglobulin (IVIG), DNA vaccination, statins, antioxidants (N-acetylcysteine (NAC), Cysteamine (CYST)), anti-IgE antibodies and anti-FcεRIα antibodies, Syk (spleen tyrosine kinase) inhibition, and Jak (Janus kinase) inhibition), kidney excision, kidney transplant.

Accordingly, the present invention comprises an anti-SLE agent for use in treating SLE wherein the dosage regime is determined based on the results of the method of the first aspect of the invention.

The present invention comprises the use of an anti-SLE agent in treating SLE wherein the dosage regime is determined based on the results of the method of the first aspect of the invention.

A second aspect of the invention provides an array for determining a systemic lupus erythematosus-associated disease state in an individual comprising one or more binding agent as defined in the first aspect of the invention.

Alternatively or additionally the array is for use in a method according to the first aspect of the invention. Alternatively or additionally the array is an array as defined in the first aspect

of the invention. Alternatively or additionally the array is capable of binding to all of the proteins defined in Table A.

A third aspect of the invention provides the use of one or more biomarkers selected from the group defined in Table A as a biomarker for determining a systemic lupus erythematosus-associated disease state in an individual. Alternatively or additionally all of the biomarkers defined in Table A are used as a biomarker for determining a systemic lupus erythematosus-associated disease state in an individual.

A fourth aspect of the invention provides the use of one or more biomarkers selected from the group defined in Table A in the manufacture of a medicament (*e.g.* a diagnostic agent) for determining a systemic lupus erythematosus-associated disease state in an individual.

A fifth aspect of the invention provides one or more biomarkers selected from the group defined in Table A for determining a systemic lupus erythematosus-associated disease state in an individual.

A sixth aspect of the invention provides use of one or more binding agent as defined in the first aspect of the invention for determining a systemic lupus erythematosus-associated disease state in an individual. Alternatively or additionally all of the biomarkers defined in Table A are used for determining a systemic lupus erythematosus-associated disease state in an individual. In one embodiment, the binding agent(s) is/are antibodies or antigen-binding fragments thereof.

A seventh aspect of the invention provides use of one or more binding agent as defined in the first aspect of the invention for the manufacture of a medicament (*e.g.* a diagnostic agent) for determining a systemic lupus erythematosus-associated disease state in an individual. In one embodiment, the binding agent(s) is/are antibodies or antigen-binding fragments thereof.

An eighth aspect of the invention provides one or more binding agent as defined in the first aspect of the invention for determining a systemic lupus erythematosus-associated disease state in an individual. In one embodiment, the binding agent(s) is/are antibodies or antigen-binding fragments thereof.

A ninth aspect of the invention provides a kit for determining a systemic lupus erythematosus-associated disease state in an individual comprising:

i) one or more binding agent or as defined in the first aspect of the invention or an array as defined in the first or second aspects of the invention, and

ii) (optionally) instructions for performing the method as defined in the first aspect of the invention.

A tenth aspect of the invention provides a method of treating systemic lupus erythematosus in an individual comprising the steps of:

(a) determining a systemic lupus erythematosus-associated disease state in an individual according to the method defined in the first aspect of the invention; and

(b) providing the individual with systemic lupus erythematosus therapy.

By "Systemic lupus erythematosus therapy" we include treatment of the symptoms of systemic lupus erythematosus (SLE), most notably fatigue, joint pain/swelling and/or skin rashes.

Other symptoms of SLE can include:

- a fever (high temperature)
- swollen lymph glands (small glands found throughout your body, including in your neck, armpits and groin)
- recurring mouth ulcers
- hair loss (alopecia)
- high blood pressure (hypertension)
- headaches and migraines
- stomach (abdominal) pain
- chest pain
- depression
- dry eyes
- memory loss
- seizures (fits)
- problems thinking clearly and difficulty telling the difference between reality and imagination (psychosis)
- shortness of breath
- Raynaud's phenomenon – a condition that limits the blood supply to your hands and feet when it is cold

- ankle swelling and fluid retention (oedema)

Typically, treatment for SLE may include one or more of the following (see also above):

(a) Limiting exposure to the sun;
(b) Vitamin D supplements;
(c) Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen;
(d) Antimalarial agents, such as hydroxychloroquine;
(e) Corticosteroids;
(f) Immunosuppressants;
(g) Rituximab; and
(h) Belimumab.

An eleventh aspect of the invention provides a computer program for operating the methods the invention, for example, for interpreting the expression data of step (c) (and subsequent expression measurement steps) and thereby diagnosing or determining a pancreatic cancer-associated disease state. The computer program may be a programmed SVM. The computer program may be recorded on a suitable computer-readable carrier known to persons skilled in the art. Suitable computer-readable-carriers may include compact discs (including CD-ROMs, DVDs, Blue Rays and the like), floppy discs, flash memory drives, ROM or hard disc drives. The computer program may be installed on a computer suitable for executing the computer program.

Preferred, non-limiting examples which embody certain aspects of the invention will now be described with reference to the following tables and figures:

Figure 1. Serum biomarker panel discriminating Active SLE vs. Normal. A) Backward elimination analysis of the training set, resulting in a condensed set of 25 antibodies (marked with an arrow) providing the best classification. B) AUC ROC curve for the test set, based on the frozen SVM model and 25-plex antibody signature. C) Principle component analysis (PCA) plot of the training set onto which the test set was then mapped. D) PCA plot of the test set only where the training set is removed from the plot for a clearer view of the separation of samples in the test set. E) Heat map for the test set, based on the 25-plex antibody signature (red – up-regulated, green –down-regulated, back – unchanged).

Figure 2. Serum biomarker panels classifying NonActive SLE vs. Normal (A-D), and Active SLE vs. NonActive SLE (E-H). A and E) AUC ROC curves for the test sets, based on the

frozen SVM models and 25-plex antibody signatures for each corresponding comparison. B and F) Principle component analysis (PCA) plots of the training sets onto which the test sets were then mapped with respect to corresponding comparison. C and G) PCA plot of the test sets only where the training sets are removed from the plots for a clearer view of the separation of samples in the test sets. D and H) Heat maps for the test sets, based on the 25-plex antibody signatures (red – up-regulated, green –down-regulated, back – unchanged).

Figure 3. Robustness of the data set on the classification of Active SLE vs. Normal (A and D), NonActive SLE vs. Normal (B and E), and Active SLE vs. NonActive SLE (C and F). A-C) Boxplots of the AUC ROC values for the test sets, based on the frozen SVM models and 25-plex antibody signatures, iterated ten times, i.e. using ten different pairs of training and test sets for each corresponding comparison. D-F) Frequencies (> 50%) at which each biomarker occurred in the ten 25-plex antibody signatures in each corresponding comparison are presented as tables.

Figure 4. A) Heat map for Active SLE vs. Normal, NonActive SLE vs. Normal, and Active SLE vs. NonActive SLE, based on the comparison of 31 non-redundant antigen proteins including the top 25 statistically differentially expressed analytes and the six significantly de-regulated proteins (based on the differences in fold change) with (red – up-regulated, green –down-regulated, back – unchanged). B) Protein expression profiles of three selected key biomarkers are shown as boxplots. The median values are indicated (thick line) and the hinges represent the 25th percentile and the 75th percentile, respectively. The protein expression levels are shown for two complement proteins (C1q and C4) and cystatin C. C) The protein expression level of complement factor C1q are shown as boxplots, when comparing NonActive SLE vs. Active SLE, with respect to array data and obtained clinic data measured by ELISA.

Figure 5. Serum biomarker panels discriminating HighActive SLE vs. Normal, and HighActive SLE vs. NonActive SLE. A) HighActive SLE vs. Normal, illustrated by ROC AUC curve and heat map (20 top differentially expressed biomarkers; red – up-regulated, green –down-regulated, back – unchanged). Normal is colored as (blue) and HighActive SLE as (green). B) HighActive SLE vs. NonActive SLE, illustrated by ROC AUC curve and heat map (20 top differentially expressed biomarkers). SLE subsets are colored as: HighActive SLE (green) and NonActive SLE (brown).

Figure 6. The protein expression levels of complement factors C4 and C1q are shown as boxplots, when comparing HighActive SLE vs. NonActive SLE, with respect to array data and obtained clinic data measured by ELISA.

Figure 7. Classification of SLE patients, grouped according to disease severity (i.e. SLE1-SLE3), using SVM leave-one-out cross-validation procedure. A) SLE1 samples were classified when comparing Active SLE vs. Normal. B) SLE2 samples were classified when comparing Active SLE vs. Normal / NonActive SLE, and NonActive SLE vs. Normal. C) SLE3 samples were classified when comparing Active SLE vs. Normal / NonActive SLE, and NonActive SLE vs. N.

Figure 8. Longitudinal analysis of SLE samples (four samples per patient (n=4; denoted A-D)) collected at four different time-points during follow-up. A-D) The top (≤ 20) deregulated expressed serum proteins were identified using multi-group comparisons, and the samples were visualized using supervised hierarchical clustering in combination with heat-maps. The disease activity status of samples were started at time 0 and the time of sample collection were recorded (≤ 3.3 years).

EXAMPLES

Introduction

Objective. To define a multiplex serum biomarker panel reflecting disease activity in systemic lupus erythematosus (SLE), taking the next steps towards serum-based detection of flares.

Methods. Affinity proteomics, represented by 195-plex recombinant antibody microarrays, targeting mainly immunoregulatory proteins, was used to perform protein expression profiling of non-fractionated, biotinylated serum samples. State-of-the-art bioinformatics was used to define biomarkers and condensed multiplex signatures mirroring disease activity in SLE.

Results. The results showed that a single drop of blood contained significant amount of biological information, in the form of immunoregulatory proteins (e.g. C1q, C3, C4, Factor B, MCP-1, CD40L, IL-1ra, IL-5, IL-12, IL-16 and IFN-γ) reflecting SLE flares that could be harvested using affinity proteomics. The first condensed ($n \leq 25$) multiplexed serum biomarker panels detecting (classifying) active SLE with high discriminatory power were deciphered. Further, the potential of the approach for serological monitoring of flares over time was indicated.

Conclusion. Our study demonstrated that the immune system could be used as a unique sensor for SLE flares. High-performing serum biomarker panels associated with SLE disease activity were identified, allowing and monitoring and forecasting of disease outbreaks.

Materials and methods

Clinical samples

In total, 197 serum samples were collected at the Department of Rheumatology, Skåne University Hospital (Lund, Sweden), including SLE patients (n=86) and normal controls (N) (n=50) (Table I). The SLE patients had clinical SLE diagnosis (22) and displayed four or more of American College of Rheumatology classification criteria (23, 24). The SLE samples were collected over time during follow-up and the patients were presented with either flare or remission, i.e. for some patients up to four samples were collected at different time-points. The SLE patients (samples) were marked according to disease phenotype (25); 1) skin and musculoskeletal involvement (SLE1, n=30); 2) serositis, systemic vasculitis but not kidney involvement (SLE2, n=30); 3) presence of SLE glomerulonephritis (SLE3, n=87).

The clinical disease activity was defined as SLE disease activity index 2000 (SLEDAI-2K) score (5). The SLE samples were grouped in three groups, according to SLEDAI-2K scores; < 5 = NonActive (n=63), >5 = Active (n=83), > 16 = HighActive (n=28). All samples were aliquoted and stored at -80°C until analysis. This retrospective study was approved by the regional ethics review board in Lund, Sweden. The serum levels of C1q and C4 were determined using rocket immunoelectrophoresis (C1q) and tubidometry (C4). The same samples have been used in a parallel, but separate study, aiming to define serum biomarkers for SLE diagnosis (Delfani *et al*, 2016, *supra*).

Labelling of serum samples

The serum samples were labelled with EZ-link Sulfo-NHS-LC-Biotin (Pierce, Rockford, IL, USA) using a previously optimized labelling protocol for serum proteomes (26-28). Briefly, the samples were diluted 1:45 in PBS (about 2mg protein/ml), and biotinylated at a molar ratio of biotin:protein of 15:1. Unreacted biotin was removed by extensive dialysis against PBS (pH 7.4) for 72 h at 4°C. The samples were aliquoted and stored at -20°C until further use.

Production and purification of antibodies

In total, 195 human recombinant single-chain fragment variable (scFv) antibodies, including 180 antibodies targeting 73 mainly immunoregulatory analytes, anticipated to reflect the events taking place in SLE, and 15 scFv antibodies targeting 15 short amino acid motifs (4 to 6 amino acids long) (29) were selected from a large phage display library (Supplementary Table I) (30) (Säll *et al*, submitted). The specificity, affinity, and on-chip functionality of the scFv antibodies have been previously validated (see Supplementary Appendix 1 for details).

All scFv antibodies were produced in *E. coli* and purified from expression supernatants using affinity chromatography on Ni^{2+}-NTA agarose (Qiagen, Hilden, Germany) validated (see Supplementary Appendix 1 for details).

Production and analysis of antibody microarrays

The scFv microarrays were produced and handled using a previously optimized and validated set-up (19) (Delfani *et al*, 2016, *supra*) (see Supplementary Appendix 1 for details). Briefly, 14 identical 25x28 subarrays were printed on each black polymer MaxiSorp microarray slide (NUNC A/S, Roskilde, Denmark) using a non-contact printer (SciFlexarrayer S11, Scienion, Berlin, Germany). Biotinylated samples were added and any bound protein antigens were visualized using Alexa 647-labelled streptavidin (SA647)

(Invitrogen). Finally, the slides were scanned with a confocal microarray scanner (ScanArray Express, PerkinElmer Life & Analytical Sciences).

Data pre-processing

The ScanArray Express software v4.0 (PerkinElmer Life & Analytical Sciences) was used to quantify spot signal intensities. Signal intensities with local background subtraction were used for data analysis. Each data point represents the mean value of all three technical replicate spots, unless any replicate CV exceeded 15%, in which case the worst performing replicate was eliminated and the average value of the two remaining replicates was used instead. Log^{10} values of signal intensities were used for subsequent analysis. The microarray data was normalized in a two-step procedure using a semi-global normalization method (19, 31, 32) and the "subtract by group mean" approach (see Supplementary Appendix 1 for details).

Data analysis

Where applicable, the sample cohort was randomly divided into a training set (2/3 of the samples) and a test set (1/3 of the samples), making sure that the distribution of SLE vs. controls and/or samples with active vs. inactive disease was similar between the two sets. It should be noted that for those SLE patients where more than one sample was at hand, the sample was randomly selected for each comparison, and only one sample per patient was included in each subset comparison in order to avoid bias (i.e. over-representation of certain patients).

The support vector machine (SVM) is a supervised learning method in R (33-35) that we used to classify the samples (see Supplementary Appendix 1 for details). For classification of HighActive SLE vs. N, HighActive SLE vs. NonActive SLE, the SVM was trained using a leave-one-out cross-validation procedure (31), and the prediction performance of the classifier was evaluated by constructing a receiver operating characteristics (ROC) curve and calculating the area under the curve (AUC).

In the case of Active SLE vs. N, NonActive SLE vs. N, and Active SLE vs. NonActive SLE, the samples were randomly divided into a training set and a test set, and a backward elimination algorithm (36) combined with a leave-one-out cross-validation procedure was applied on the training set to determine a condensed panel of antibodies displaying the highest combined discriminatory power. A single SVM model was then calibrated on the training set using the condensed antibody panel, where after the classifier was frozen and evaluated on the test set. This process was iterated nine additional times, in nine different,

randomly generated pairs of training sets and test sets, with subsequent generation of ROC AUC curves. In the end, a median AUC value was calculated based on all ten runs, and used as a measure of the accuracy of the biomarker signatures in the tests.

To investigate whether phenotype was a confounding factor for classification of Active SLE vs. N and NonActive SLE vs. N, the SLE samples were also grouped according to phenotype (SLE1, SLE2, and SLE3) and the above analysis were re-run.

Significantly differentially expressed analytes ($p < 0.05$) were identified based on t-tests when performing two-group comparisons. Longitudinal analysis of SLE samples were conducted using multi-group comparison. Heat maps and visualization of the samples by principal component analysis (PCA) were carried using Qlucore Omics Explorer 2.2. (Qlucore AB, Lund, Sweden).

Supplementary materials and methods

Production and purification of antibodies

In total, 195 human recombinant scFv antibodies, including 180 antibodies targeting 73 mainly immunoregulatory analytes, anticipated to reflect the events taking place in SLE, and 15 scFv antibodies targeting 15 short amino acid motifs (4 to 6 amino acids long) (1) were selected from a large phage display library (Supplementary Table I) (2) (Säll *et al*, unpublished data). The specificity, affinity (normally in the nM range), and on-chip functionality of these phage display derived scFv antibodies was ensured by using i) stringent phage-display selection and screening protocols (2), ii) multiple clones (1-9) per target, and iii) a molecular design, adapted for microarray applications (3). In addition, the specificity of several of the antibodies have previously also been validated using well-characterized, standardized serum samples (with known analytes of the targeted analytes), and orthogonal methods, such as mass spectrometry (affinity pull-down experiments), ELISA, MesoScaleDiscovery (MSD) assay, cytometric bead assay, and MS, as well as using spiking and blocking (Supplementary Table I) (4-12). Notably, the reactivity of some antibodies might be lost since the label (biotin) used to label the sample to enable detection could block the affinity binding to the antibodies (epitope masking). However, we addressed this potential problem by frequently including more than one antibody clone against the same protein, but directed against different epitopes (3).

All scFv antibodies were produced in 100 ml *E. coli* and purified from expression supernatants using affinity chromatography on Ni^{2+}-NTA agarose (Qiagen, Hilden,

Germany). ScFvs were eluted using 250 mM imidazole, extensively dialyzed against PBS (pH 7.4), and stored at 4°C until use. The protein concentration was determined by measuring the absorbance at 280nm (average 340 µg/ml, range 30-1500 µg/ml). The degree of purity and integrity of the scFv antibodies was evaluated by 10% SDS-PAGE (Invitrogen, Carlsbad, CA, USA).

Production and analysis of antibody microarrays

The scFv microarrays were produced using a previously optimized and validated set-up (9) (Delfani *et al*, unpublished data). Briefly, the antibodies were printed on black polymer MaxiSorp microarray slides (NUNC A/S, Roskilde, Denmark), by spotting one drop (~330 pL) at each position, using a non-contact printer (SciFlexarrayer S11, Scienion, Berlin, Germany). Each microarray, composed of 195 scFvs antibodies, one negative control (PBS) and one positive control (biotinylated BSA, b-BSA), was split into 14 sub-arrays of 25x28 spots. Furthermore, each sub-array was divided in three segments where a row of b-BSA consisting of 25 replicate spots was printed at the beginning and the end of each segment. Each scFv antibody was dispensed in three replicates, one in each segment, to assure adequate reproducibility.

For handling the arrays, we used a recently optimized protocol (Delfani *et al*, unpublished data). Briefly, the printed microarrays were allowed to dry for 2h at RT and were then mounted in a multi-well incubation chambers (NEXTERION® IC-16) (Schott, Jena, Germany). Next, the slides were blocked with 1% (v/v) Tween-20 (Merck Millipore) and 1% (w/v) fat-free milk powder (Semper, Sundbyberg, Sweden) in PBS (MT-PBS solution) for 2h at RT. Subsequently, the slides were washed for four times with 150 µl 0.05% (v/v) Tween-20 in PBS (T-PBS solution), and then incubated with 100 µl biotinylated serum sample, diluted 1:10 in MT-PBS solution (corresponding to a total serum dilution of 1:450), for 2h at RT under gentle agitation using an orbital shaker. After another washing, the slides were incubated with 100 µl 1µg/ml Alexa 647-labelled streptavidin (SA647) (Invitrogen) in MT-PBS for 1h at RT under agitation. Finally, the slides were washed in T-PBS, and dried under a stream of nitrogen gas, and immediately scanned with a confocal microarray scanner (ScanArray Express, PerkinElmer Life & Analytical Sciences) at 10 µm resolution, using fixed scanner settings of 60% PMT gain and 90% laser power.

Data pre-processing

The ScanArray Express software v4.0 (PerkinElmer Life & Analytical Sciences) was used to quantify spot signal intensities, using the fixed circle method. Signal intensities with local background subtraction were used for data analysis. Each data point represents the mean

value of all three replicate spots, unless any replicate CV exceeded 15%, in which case the worst performing replicate was eliminated and the average value of the two remaining replicates was used instead. Log^{10} values of signal intensities were used for subsequent analysis.

For evaluation of normalization strategies and initial analysis on variance, the data was visualized using principal component analysis (PCA) and hierarchical clustering In Qluecore Omics Explorer (Qlucore AB, Lund, Sweden). Subsequently, the data normalization procedure was carried out in two steps. First, the microarray data was normalized for array-to-array variations using a semi-global normalization method, where 20% of the analytes displaying the lowest CV-values over all samples were identified and used to calculate a scaling factor, as previously described (9, 13, 14). Second, the data was normalized for day-to-day variation using the "subtract by group mean" approach. In this approach, the mean value ($\bar{x}$) of each analyte (i) within each day of analysis was calculated (= $\bar{x}_i$), and subtracted from the respective individual values (x_i), thus zero centering the data (= x_i-$\bar{x}_i$). Finally, the global mean signal for each antibody was calculated and added to each respective data point in order to avoid negative values in the data set.

Data analysis

The support vector machine (SVM) is a supervised learning method in R (15-17) that was used to classify the samples. The supervised classification was conducted using a linear kernel, and the cost of constraints was set to 1, which is the default value in the R function SVM, and no attempt was performed to tune it. This absence of parameter tuning was chosen to avoid over fitting. No filtration on the data was done before training the SVM, i.e. all antibodies used on the microarray were included in the analysis. Further, a receiver operating characteristics (ROC) curve, as constructed using the SVM decision values and the area under the curve (AUC), was calculated.

The samples were first randomly divided into a training set (2/3 of the data) and a test set (1/3 of the data) while maintaining the same ratios of samples from each group. It should be noted that for those SLE patients where more than one sample was at hand, the sample was randomly selected for each comparison, and only one sample per patient was included in each subset comparison in order to avoid bias. A backward elimination algorithm (18) combined with a leave-one-out cross-validation procedure was then applied to the training set to create a condensed panel of antibodies displaying the highest combined discriminatory power. The condensed panel of antibodies was then employed to train a single SVM model on the training set. The trained SVM model was then frozen and applied

to the test set, and a ROC AUC was calculated and used to evaluate the performance of the SVM classifier. In order to demonstrate the robustness of the data set, 9 additional training and test sets were generated and the above data analysis process was repeated. Finally, the frequency at which each antibody was included in all 10 different defined antibody panels was assessed.

The SVM was trained using the leave-one-out cross-validation procedure as previously described (13). By iterating all samples, a ROC curve was constructed using the decision values and the corresponding AUC value was determined, and used for evaluating the prediction performance of the classifier.

Significantly differentially expressed analytes ($p < 0.05$) were identified based on t- tests. Heat maps and visualization of the samples by principal component analysis (PCA) were carried using Qlucore Omics Explorer.

Results

In this study, we have used recombinant scFv antibody microarrays for pin-pointing serum biomarker panels reflecting disease activity in SLE. A total of 197 biotinylated serum samples (SLE n=147, normal controls n=50) representing 136 patients (86 SLE and 50 controls) (Table I) were profiled using 195-plex antibody microarrays, targeting mainly immunoregulatory analytes. The generated microarray images were transformed into protein expression profiles, or protein maps, and SLE-associated serum biomarkers were deciphered.

<u>Profiling of active SLE</u>

To decode serum biomarkers reflecting active SLE, we first investigated whether SLE patients with active disease (denoted Active SLE) vs. normal controls could be discriminated. To this end, the data set was randomly divided into a training set (2/3 of all samples) and a test set (1/3 of all samples). A stepwise backward elimination procedure was then applied to the training set in order to identify the smallest set of antibodies, i.e. biomarkers, required for differentiating Active SLE vs. normal controls. The results showed that a combination of 10 antibodies, evaluated in terms of the smallest error, provided the best classification (Fig. 1A). But in order to allow some flexibility in the signature, the top 25 antibodies were selected to represent a condensed biomarker panel (Fig. 1A).

In order to evaluate the classification power of this 25-plex biomarker signature, the panel was first used to train a single SVM model, denoted frozen SVM, on the training set. Next,

the frozen SVM model was applied to the independent test set. The results showed that a ROC AUC value of 0.96 was obtained (Fig. 1B), demonstrating that Active SLE vs. normal controls could be differentiated with a high discriminatory power. Visualizing the data using a principle component analysis (PCA) based approach, a similar distinct discrimination was observed (Figs. 1C and 1D). A heat map for the test set, based on the 25-plex signature, is shown in Figure 1E. The biomarker panel was found to be composed of both up- (e.g. IL-6, IL-8, MCP-1, and TNF-α) and down-regulated proteins (e.g. C3), although the former dominated. It should be noted that we did not differentiate whether the observed up- and down-regulated levels of a protein was due to an in-/decreased production or in-/decreased consumption. Hence, the results showed that a multiplexed, discriminatory biomarker panel reflecting active SLE could be deciphered from crude serum.

Profiling of NonActive SLE

Next, we focused on SLE patients at remission (denoted NonActive SLE). As above, the samples were randomly divided into a training set and test set, whereafter a condensed 25-plex biomarker signatures discriminating NonActive SLE vs. normal controls was defined and used to train a frozen SVM model (training set). Subsequently, the model was evaluated using the independent test set. The results showed that a ROC AUC value of 0.89 was obtained (Fig. 2A), demonstrating that NonActive SLE vs. normal controls could be differentiated. PCA-based analysis showed that a similar distinct discrimination was obtained (Figs. 2B and 2C). A heat map for the test set, based on the 25-plex signature, is shown in Figure 2D. The panel was found to be composed of both up- (e.g. IL-6, IL-18, and TNF-α) and down-regulated proteins (e.g. C3 and C4), but the former dominated. Thus, the data demonstrated that a multiplexed, discriminatory panel of biomarkers reflecting also NonActive SLE could be defined from crude serum.

Profiling of NonActive SLE and Active SLE

Next, we compared the serum protein expression profiles of NonActive SLE (SLEDAI-2K: mean 2, range 0-5) and Active SLE(SLEDAI-2K: mean 13, range 6-32). Using the same stringent bioinformatics approach as above, a condensed 25-plex serum biomarker signature discriminating NonActive SLE vs. Active SLE with a ROC AUC value of 0.83 was deciphered (Fig. 2E). A similar distinct discrimination was observed using PCA-based analysis (Figs. 2F and 2G). The panel, illustrated as a heat map in Figure 2H, was found to be composed of cytokines (e.g. IL-16 and IFN-γ), complement proteins (e.g. C4 and Factor B), soluble surface proteins (e.g. CD40 and CD40L) as well as other proteins (e.g. IgM). Taken together, the results thus showed that a multiplexed panel of serum biomarkers

discriminating NonActive SLE vs. Active SLE, i.e. reflecting disease activity, could be delineated.

Robustness of the classifications

To test the robustness of the data set with respect to the above classifications, we randomly divided the entire data set in 9 additional pairs of training and test sets, and re-ran all three of the above comparisons. The results showed that all 10 comparisons resulted in a median ROC AUC value of 0.94 (range 0.83-0.98) for Active SLE vs. controls (Fig. 3A), 0.77 (0.65-0.98) for NonActive SLE vs. controls (Fig. 3B), and 0.72 (0.59-0.88) for Active SLE vs. NonActive SLE (Fig. 3C). Thus, the data indicated that the power and robustness of the classification varied, and decreased in the order of Active SLE vs. N (high) > NonActive SLE vs. N (medium to high), and Active SLE vs. NonActive SLE (low to medium). Apart from illustrating the robustness of the data, it also outlined the importance of how the samples were divided on the subsequent data analysis.

Furthermore, the frequency at which each biomarker occurred in these ten 25-plex signatures is shown in Figures 3D to 3F for all markers present six or more times. The data showed that the identity of the top markers varied, as could be expected, but that a core of 8 biomarkers were constant (present in at least 8 of 10 signatures) and highly overlapping (Cystatin C, Sialle x, C3, CD40, TGF-β1, and MCP-1) between Active SLE vs. Normal and NonActive SLE vs. Normal. In contrast, only three core biomarkers (Factor B, Cystatin C, and C1q) were pinpointed for Active SLE vs. NonActive SLE. Of note, the latter classification also resulted in the lowest median ROC AUC value (cfs. Figs. 3A to 3C). This could indicate a more pronounced impact of biological heterogeneity among, in particular the active SLE patients, on the process of defining serum biomarkers reflecting disease activity. In more detail, how the samples were divided between the training and test sets will more likely play a key role in this particular biomarker identification process, since SLE patients can display similar disease activity in terms of SLEDAI-2K, but based on very different biological (clinical) features.

Biomarkers reflecting the biology of disease activity

Since the biology of disease activity will not only be reflected by biomarkers identified as being best suited for classification based on backward elimination (see above), we also addressed biomarkers identified as being significantly differentially expressed ($p < 0.05$) based on signal intensities and/or fold changes. To this end, the combined non-redundant top 31 differentially expressed biomarker list for Active SLE vs. Normal, NonActive SLE vs. Normal, and Active SLE vs. NonActive SLE is shown in Figure 4A. Interestingly, a variety

of biomarkers were found to be de-regulated, such as soluble cytokine receptors (e.g. IL-1ra), cytokines (IL-16, and IFN-γ), soluble surface proteins (e.g. CD40), complement proteins (e.g. C1q, C3, and C4), and several other proteins (e.g. Cystatin C and IgM). The de-regulated patterns of C1q, C4, and cystatin C is highlighted (Fig. 4B). Thus, the results showed that a multiplexed panel of deregulated biomarkers reflecting SLE disease activity could be deciphered.

Next, C1q was selected in an attempt to validate the array findings using an orthogonal method. To this end, the levels of C1q, as determined using our recombinant antibody arrays, were compared to those obtained using a clinically implement method (rocket immunoelectrophoresis) (Fig. 4C). The results showed that a similar pattern of de-regulated levels of C1q was observed for Active SLE vs. NonActive SLE. Hence, the observed array data for C1q was validated using an orthogonal method.

Refined biomarkers reflecting high disease activity

To find better biomarkers reflecting disease activity, SLE patients displaying high activity (in terms of SLEDAI-2K) were selected (denoted HighActive SLE) (SLEDAI-2k ≥16) and their serum protein profiles were re-compared to those of normal controls and NonActive SLE. The classification was performed adopting a leave-one-out cross-validation, the most stringent approach that can be employed when the sample cohorts were too small to justify the samples to be split into training and test sets.

The results showed that a ROC AUC value of 0.98 was obtained (Fig. 5A), demonstrating that HighActive SLE vs. normal controls could be differentiated with a high discriminatory power. The top 20 significantly differentially expressed ($p < 0.05$) proteins are shown as a heat map (Fig. 4A). The biomarker list contained variety of de-regulated proteins, such as soluble cytokine receptors (e.g. IL-1ra), cytokines (IL-2, IL-8, IL-18, and MCP-1), complement proteins (e.g. C1 esterase inhibitory), and several other proteins (e.g. Cystatin C, Sialle x, and IgM). Of note, several antibodies directed against the same protein, but targeting different epitopes, gave similar results, further supporting the observations.

In comparison, HighActive SLE vs. NonActive SLE displayed a ROC AUC value of 0.87, also indicating a high discriminatory power (Fig. 5B). Compared to HighActive SLE vs. normal controls, the top 20 significantly differentially expressed ($p < 0.05$) proteins were, as could be expected, found to display a less distinct heat map (cfs. Figs. 5A and 5B). Among the de-regulated biomarkers, a range of proteins were observed, such as soluble cytokine receptors (e.g. IL-1ra), cytokines (IL-2, IL-5, IL-12, and MCP-1), complement proteins (e.g.

C4 and C1q), and several other proteins (e.g. Cystatin C and Sialle x). Again, the observations were supported by the fact that several antibodies directed against the same protein gave similar profiles. To further support the data, two proteins (C4 and C1q), were selected, and their expression profiles were compared to those determined using orthogonal methods (rocket immunoelectrophoresis (C1q) and tubidometry (C4)). The data showed that the protein expression profiles, obtained using antibody microarrays, could be validated in both cases (Figure 6).

Importance of phenotype

Disease phenotype could be one, of several, potential confounding factors, in defining serum biomarkers reflecting SLE disease activity. In an attempt to address this, the samples were also grouped according to phenotype (SLE1, SLE2, and SLE3) and parts of the classifications were re-run (for those groups where sufficient number of samples were still obtained). The classifications were performed adopting a leave-one-out cross-validation.

The results showed Active SLE vs. normal controls could be discriminated with a high ROC AUC value independent of phenotype (SLE1 - 0.95; SLE2 - 0.95; SLE3 - 0.98) (Fig. 7). Similarly, NonActive SLE vs. normal controls could also be discriminated irrespective of phenotype (SLE2 - 0.090; SLE3 - 0.78) (Figs. 7B and 7C). Finally, Active SLE vs. NonActive SLE could also be classified irrespective of disease phenotype, albeit with lower ROC AUC values (SLE2 - 0.79; SLE3 - 0.69). Hence, the data indicated that phenotype was not a key confounding factor for pinpointing multiplexed serum biomarkers mirroring disease activity.

Monitoring of disease activity over time

Finally, in a first attempt to explore whether SLE disease activity could be monitored over time, a limited set of longitudinal samples were profiled. To this end, 4 patients were selected as showcase, and 4 serum samples per patient were collected over time (within ≤ 3.3. years) at flares and remissions (3 Active vs. 1 NonActive, 2 Active vs. 2 NonActive, or 1 Active vs. 3 NonActive). For each patient, the top ≤ 20 de-regulated proteins were identified using multi-group comparisons, and the samples were visualized using supervised hierarchical clustering in combination with heat-maps (Fig. 8). A variety of de-regulated proteins were indicated, including cytokines (e.g. IL-10, IL-12, IL-18, IFN-γ, and MCP-1), complement proteins (e.g. C3, C4, and C5), soluble surface proteins (e.g. CD40), as well as other proteins (e.g. IgM and Sialle x). As before, these pilot observations were supported by that several antibodies directed against the same protein, but targeting different epitopes, gave similar profiles. For all 4 patients, the samples clustered as two groups, Active vs. NonActive, meaning that the longitudinal samples collected ate flares

were more similar to each other than to those collected at remission, and vice versa. This further supports the notion that crude serum contains information (biomarkers) reflecting disease activity that could be harvested using affinity proteomics, indicating the potential for monitoring disease activity over time.

Discussion

Biomarkers that could be used to detect, monitor, and/or even forecast SLE flares would be a very valuable clinical tool (9, 11). Despite major efforts, it is clear that the quest for such high-performing markers, preferentially based on a blood test, is still at an early stage (37). Since we can only manage what we can measure, additional and/or refined methodologies for protein expression profiling of crude clinical samples will be essential. Here, we have expanded previous efforts (19, 20) (Nordström *et al*, submitted; Delfani *et al*, 2016, *supra*), and further showed that a single drop of blood harboured significant amount of SLE related information, in the format of relevant biological biomarkers, that could be harvested, using recombinant antibody microarrays.

25-plex panels of biomarkers reflecting SLE disease activity (and SLE) were defined, including group of proteins such as complement proteins (e.g. C1q, C1 esterase inhibitor, C3, C4, C5, and Factor B), cytokines (e.g. IL-1ra, IL-2, IL-5, IL-6, IL-8, IL-12, IL-16, IL-18, IFN-γ, MCP-1, TGF-β1, and TNF-α), cytokine receptors (cytokines (e.g. IL1ra), soluble surface proteins (e.g. CD40 and CD40L), and other proteins (e.g. Cystatin C, Sialle x, and IgM). These biomarker panels could be used to classify active SLE, although the power of classification varied from high (ROC AUC of 0.98) to low (AUC of 0.69) depending the precise comparison at hand. In agreement, some of these markers have in previous work also been found to be associated with SLE flares (and/or SLE per see), see e.g. (4, 7-11, 38, 39). But the markers were then mainly explored as single biomarkers and/or low-plex panels, displaying varying (low) performance.

When comparing the core of the 8 most robust (frequently occurring) markers for Active SLE vs. N with NonActive SLE vs. N, 6 of 8 biomarkers were found to overlap (Cystatin C, Sialle x, CD40, TGF-β1, C3, and MCP-1). Serum Cystatin C is a biomarker that has been found to be associated with renal impairment in SLE, and thus deregulated in SLE (40, 41). Imbalance of T-helper subsets (TH1, TH2, and TH17) and regulatory T-cells has been suggested to contribute to the pathogenesis of SLE (42). In such context, sialle x, or sialyl lewis x, has been shown to identify highly differentiated and most suppressive $FXP3^{high}$ regulatory T cells involved in flares (43). Deregulated levels of CD40 has been observed in SLE, and autoreactive B cells and its abnormal CD40 signalling play important roles in the

pathogenesis of SLE (44). Of note, de-regulated levels of CD40L, which binds to CD40, has also been frequently observed and correlated with SLE disease activity (45). In fact, CD40L was differentially expressed when comparing Active SLE vs. NonActive SLE. Further, deregulated serum levels of TGF-β1 has been shown to be associated with renal damage in SLE, in particular for patients with high disease activity (46). Altered levels of several complement proteins, including C3, has often been used as a marker for disease activity (47). MCP-1 is a leukocyte chemotactic factor that has been associated with renal injury, poor prognosis, and disease activity (48). Hence, the biomarkers of this core overlap were found to be biologically relevant markers.

Instead, focusing on the serum signature discriminating Active SLE vs. NonActive SLE, the core of 3 most robust (frequently occurring) included Factor B, C1q, and Cystatin C. Factor B is often used as an indicator for alternative pathway activation of the complement system. Notably, previous work has shown Factor B activation products in SLE to be marker(s) of severe disease activity (49). Furthermore, the levels of classical complement pathway components, such as C1q, have often been found to be altered in patients with severe disease and high disease activity (47). When reviewing the remaining seven most robust (frequently occurring) biomarkers reflecting disease activity, at least five (MCP-1, IL-9, IL-5, IL-1β, and CD40) have been shown to be associated with SLE and reflect disease activity (44, 48, 50-52). While RANTES have been shown to be associated with SLE, no correlation with disease activity has yet been confirmed (53). In our study, RANTES was indicated in the core signature reflecting flares 7 of 10 times. Several serum biomarkers reflecting flares were detected, outlining the potential of the approach. Notably, additional biomarkers (e.g. IL1-ra, IL-2, and IL-12), á priori known to be associated with SLE disease activity (11, 39, 54), were delineated when the group of SLE patients with active disease were reduced to those with high activity only. Although the precise role of IL-11 in SLE is yet unknown, considering its similarities with IL-6, it could lead to a lupus flare.

While this study showed that flares could be detected, it is limited by the fact that only the endpoints, remission vs. "full flare", were studied. As a limited showcase, we analyzed 4 patients with 4 samples each collected over time at flares and/or remissions. While the sample set is too small to draw definite conclusions, it indicated the potential of using the approach for monitoring flares over time. It will, however, be required to profile larger independent sample cohorts, composed of many well-characterized patients, each with numerous samples collected over time at frequent time-points at flares and/or remissions to demonstrate and establish serological-based tests for monitoring and potentially even

forecasting of flares in a stringent manner. The clinical impact of such potential tests are, however, significant.

Taken together, in this study we have shown that condensed (n ≤ 25), multiplexed panels of serum biomarkers detecting, and monitoring, SLE flares could be delineated.

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Tables

Table A – Core, preferred and optional biomarkers for determining a systemic lupus erythematosus-associated disease state

	Biomarker	Exemplary sequence(s)
I - core		
1	CHX10 (3)	P58304
2	LUM	P51884
3	Cyst. C	P01034
II - preferred		
4	ATP5B (2)	P06576
5	Beta-galactosidase	P16278
6	DUSP9	Q99956
7	MYOM2 (1)	P54296
8	PSA	P07288
9	Sox11a	P35716
10	Surface Ag X	NA
11	TBC1D9 (2)	Q6ZT07
12	IL-1 alpha	P01583
13	IL-1 beta	P01584
14	Motif (13)	SGSG-QEASFK (-COOH) **[SEQ ID NO: 1]**
15	Motif (14)	SGSG-EDFR (-COOH) **[SEQ ID NO: 2]**
16	Motif (3)	SGSG-DFAEDK (-COOH) **[SEQ ID NO: 3]**
17	Motif (4)	SGSG-TEEQLK (-COOH) **[SEQ ID NO: 4]**
18	Motif (5)	SGSG-LSADHR (-COOH) **[SEQ ID NO: 5]**
19	Motif (7)	SGSG-TEEQLK (-COOH) **[SEQ ID NO: 4]**
20	Motif (8)	SGSG-TEEQLK (-COOH) **[SEQ ID NO: 4]**
III - optional		
21	Angiomotin (1)	Q4VCS5
22	APOA1 (1)	P02647
23	BTK (1)	Q06187
24	C1 est. inh. (3)	P05155
25	C1q	P02745/6/7
26	C1s	P09871
27	C3	P01024
28	C4	P0COL4/5
29	C5 (1)	P01031
30	CD40	Q6P2H9
31	CD40 ligand	P29965

	Biomarker	Exemplary sequence(s)
32	Eotaxin (3)	P51671
33	Factor B	P00751
34	GLP-1	P01275
35	GM-CSF	P04141
36	HLA-DR/DP	P01903/P01911/P79483/P13762/Q30154/P20036/P04440
37	ICAM-1	P05362
38	IFN-gamma (1)	P01579
39	IgM	e.g. P01871 (not complete protein); isotype-specific for IgM on Ramos B cells)
40	IL-10 (1)	P22301
41	IL-11 (1)	P20809
42	IL-12 (1)	P29459/60
43	IL-13 (1)	P35225
44	IL-16 (1)	Q14005
45	IL-18	Q14116
46	IL-1ra	P18510
47	IL-2 (2)	P60568
48	IL-3	P08700
49	IL-4	P05112
50	IL-5	P05113
51	IL-6	P05231
52	IL-7	P13232
53	IL-8	P10145
54	IL-9	P15248
55	Integrin alpha-10	O75578
56	JAK3	P52333
57	LDL (1)	P04114
58	Leptin	P41159
59	Lewis x (1)	NA
60	MCP-1	P13500
61	MCP-3 (1)	P80098
62	MCP-4 (2)	Q99616
63	Procathepsin W	P56202
64	RANTES	P13501
65	Sialle x	NA
66	TGF-beta1	P01137
67	TNF-alpha (1)	P01375
68	TNF-beta	P01374
69	VEGF (1)	P15692

Table B – Biomarkers for determining a systemic lupus erythematosus-associated disease state

	Biomarker	AvN	NAvN	AvNA	HAvN	HAvNA
I						
1	**Cyst. C**	x	x	x	x	x
2	MCP-1	x	x	x	x	x
3	Sialle x	x	x	x	x	x
II						
4	C1 est. inh. (3)	x	x	x	x	
5	IgM	x	x	x	x	
6	TNF-beta	x	x	x	x	
III						
7	C1q	x	x	x		x
8	C4	x	x	x		x
IV						
9	IL-11 (1)	x		x	x	x
10	IL-1ra	x		x	x	x
V						
11	**IL-1 beta**	x	x	x		
12	CD40	x	x	x		
13	Factor B	x	x	x		
14	Integrin alpha-10	x	x	x		
VI1						
15	**CHX10 (3)**	x			x	x
16	IL-8	x			x	x
VII						
17	IL-5		x	x		x

	Biomarker	AvN	NAvN	AvNA	HAvN	HAvNA
VIII						
18	IL-9	x		x		x
IX						
19	LDL (1)	x	x			x
X						
20	C3	x	x			
21	IL-6	x	x			
22	GLP-1	x	x			
23	TGF-beta1	x	x			
24	TNF-alpha (1)	x	x			
25	APOA1 (1)	x	x			
26	VEGF (1)	x	x			
XI						
27	**LUM**	x		x		
28	**Motif (4)**	x		x		
29	**PSA**	x		x		
30	GM-CSF	x		x		
31	IFN-gamma (1)	x		x		
32	IL-13 (1)	x		x		
33	IL-16 (1)	x		x		
34	RANTES	x		x		
XII						
35	**ATP5B (2)**		x		x	
36	**IL-1 alpha**		x		x	
37	IL-18		x		x	
38	IL-12 (1)				x	x
39	IL-2 (2)				x	x

	Biomarker	AvN	NAvN	AvNA	HAvN	HAvNA
XIV						
40	**Motif (14)**	x			x	
XV						
41	**Motif (3)**		x	x		
XVI						
42	**Motif (5)**	x				
43	**Motif (7)**	x				
44	**TBC1D9 (2)**	x				
45	Eotaxin (3)	x				
46	IL-3	x				
47	IL-4	x				
48	MCP-4 (2)	x				
49	Procathepsin W	x				
XVII						
50	**DUSP9**			x		
51	Angiomotin (1)			x		
52	CD40 ligand			x		
53	JAK3			x		
54	**Beta-galactosidase**			x		
55	**Motif (8)**			x		
56	**Sox11a**			x		
57	**Surface Ag X**			x		
58	BTK (1)			x		
59	C1s			x		
60	C5 (1)			x		
61	HLA-DR/DP			x		

	Biomarker	AvN	NAvN	AvNA	HAvN	HAvNA
62	ICAM-1			x		
63	IL-10 (1)			x		
64	IL-7			x		
65	Leptin			x		
66	Lewis x (1)			x		
67	MCP-3 (1)			x		
XVIII						
68	**Motif (13)**				x	
XIX						
69	**MYOM2 (1)**					x

Table 1. Demographic data of SLE patients and normal controls included in the study.

Parameter	SLE	Normal controls
No. of patients	86	50
No. of serum samples	147*	50
Gender (female:male ratio)	(76:10)	(48:2)
Mean age (range)	39 (18-72)	48 (19-68)
SLEDAI-2K, mean (range), - All	8 (0-32)	n.a
- All - Active	13 (6-32)	
- Active - NonActive	2 (0-5)	

	SLE1	SLE2	SLE3**
No. of SLE samples / phenotype	30	30	87
No. of NonActive (SLEDAI $\leq$ 5)	15	18	30
No. of Active (SLEDAI > 5)	15	12	56
No. of HighActive (SLEDAI $\geq$ 16)	1	3	24

*The samples were collected over time during follow-up and the patients were presented with either flare or remission, i.e. for some patients up to four samples were collected at different time-points.

**One SLE3 sample lacked clinical information on disease activity status.

Table 2. 30 most frequent markers for the 3 main comparisons

Active SLE vs Normal		NonActive SLE vs Normal		Active SLE vs NonActive SLE	
Analytes	**Iterations (%)**	**Analytes**	**Iterations (%)**	**Analytes**	**Iterations (%)**
Cyst. C	**100**	C3	**100**	Factor B	**100**
IL-1ra	**100**	C4	**100**	C1q	80
C3	90	Cyst. C	**100**	Cyst. C	80
CD40	90	MCP-1	**100**	RANTES	70
Sialle x	90	Sialle x	90	CD40	60
IL-3	80	CD40	80	GM-CSF	60
MCP-1	80	IgM	80	IL-1β	60
TGF-β1	80	TGF-β1	80	IL-5	60
C4	70	C1 est. inh.	60	IL-9	60
Motif (4)	70	Factor B	60	MCP-1	60
IL-4	70	IL-18	60	BTK	50
IL-6	70	IL-1α	60	C3	50
IL-8	70	Angiomotin	50	IL-18	50
LUM	70	IL-6	50	IL-1ra	50
TNF-α	70	S Ag X	50	IL-3	50
IgM	60	IL-12	40	IL-8	50
Procathepsin W	60	IL-13	40	LUM	50
RANTES	60	IL-1β	40	MCP-4	50
C1q	50	TNF-β	40	Sialle x	50
Factor B	50	APOA1	30	TNF-β	50
Motif (5)	50	ATP5B	30	APOA4	40
LDL	50	C1q	30	C1 est. inh.	40
APOA1	40	Motif (14)	30	C4	40
GLP-1	40	GLP-1	30	C5	40
TNF-β	40	IL-2	30	CD40 ligand	40
APOA4	30	IL-3	30	Motif (3)	40
Motif (7)	30	IL-5	30	IL-16	40
GM-CSF	30	IL-9	30	IL-4	40
IL-13	30	Integrin α-10	30	JAK3	40
IL-18	30	OSBPL3	30	$Lewis^y$	40

Supplementary Table 1. Antigens targeted on the antibody microarray[a)]

Protein	Full name	No of antibody clones
Angiomotin	Angiomotin	2
APOA1	Apolipoprotein A1	3
APOA4	Apolipoprotein A4	3
ATP5B	ATP synthase subunit beta, mitochondrial	3
Beta-galactosidase	Beta-galactosidase	1
BTK	Tyrosine-protein kinase BTK	1
C1 est. inh.	Plasma protease C1 inhibitor	4
C1q*	Complement C1q	1
C1s	Complement C1s	1
C3*	Complement C3	6
C4*	Complement C4	4
C5*	Complement C5	3
CD40	CD40 protein	4
CD40 ligand	CD40 ligand	1
CHX10	Visual system homeobox 2	3
CT	Cholera toxin subunit B (Control)	1
Cyst. C	Cystatin-C	4
Digoxin	Digoxin	1
DUSP9	Dual specificity protein phosphatase 9	1
Eotaxin	Eotaxin	3
Factor B*	Complement factor B	4
GLP-1	Glucagon-like peptide-1	1
GLP-1 R	Glucagon-like peptide 1 receptor	1
GM-CSF	Granulocyte-macrophage colony-stimulating factor	3
HLA-DR/DP	HLA-DR/DP	1
ICAM-1	Intercellular adhesion molecule 1	1
IFN-gamma	Interferon gamma	3
IgM	Immunoglobulin M	5
IL-1 alpha*	Interleukin-1 alpha	3
IL-1 beta	Interleukin-1 beta	3
IL-10*	Interleukin-10	3
IL-11	Interleukin-11	3
IL-12*	Interleukin-12	4
IL-13*	Interleukin-13	3
IL-16	Interleukin-16	3
IL-18	Interleukin-18	3
IL-1ra	Interleukin-1 receptor antagonist protein	3
IL-2	Interleukin-2	3
IL-3	Interleukin-3	3
IL-4*	Interleukin-4	4
IL-5*	Interleukin-5	3
IL-6*	Interleukin-6	4
IL-7	Interleukin-7	2
IL-8*	Interleukin-8	3
IL-9	Interleukin-9	3
Integrin alpha-10	Integrin alpha-10	1
Integrin alpha-11	Integrin alpha-11	1
JAK3	Tyrosine-protein kinase JAK3	1
LDL	Apolipoprotein B-100	2
Leptin	Leptin	1
Lewisx	Lewis x	2
Lewisy	Lewis y	1
LUM	Lumican	1
MCP-1*	C-C motif chemokine 2	9

MCP-3	C-C motif chemokine 7	3
MCP-4	C-C motif chemokine 13	3
Motif	Peptide motifs	15
MYOM2	Myomesin-2	2
ORP-3	Oxysterol-binding protein-related protein 3	2
Procathepsin W	Procathepsin W	1
Properdin*	Properdin	1
PSA	Prostate-specific antigen	1
RANTES	C-C motif chemokine 5	3
Sialle x	Sialyl Lewis x	1
Sox11a	Transcription factor SOX-11	1
Surface Ag X	Surface Ag X	1
TBC1D9	TBC1 domain family member 9	3
VEGF*	Vascular endothelial growth factor	4

[a)]The specificity, affinity (normally in the nM range), and on-chip functionality of all of these phage display derived scFv antibodies were ensured by using i) stringent phage-display selection and screening protocols (using different sample formats, ranging from pure proteins and mixtures of pure proteins to crude samples) (16), ii) multiple clones (1 to 9) per protein, and iii) a molecular design, adapted for microarray applications (1-3) (Säll *et al* unpublished observations). In addition, the specificity of several selected antibodies (marked with an *) have been further validated using pure proteins, mixtures of pure proteins, as well as well-characterized, standardized serum samples (with known levels of the targeted analytes, spiked with known level of specific protein(s) and/or specific protein(s) depleted), and/or orthogonal methods, such as mass spectrometry (affinity pull-down experiments), ELISA, MesoScaleDiscovery assay, and cytometric bead assay, as well as using blocking experiments (4-12).

Table C – Amino acid sequences of the scFv antibodies used in the Examples

Ab	Full protein Sequence (VH-linker-VL-tag)
IL-1α (1)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSSGYYSWAFDIW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGRNTVNWYQQLPGTAPKLLIYGNSNRPSXVPDRFSGSKSGTSASLAISGLRSEDEADYY CAAWDDSLNGWAFGGXTKLTVLGEQKLISXXXLSGSAA **[SEQ ID NO:6]**
IL-1α (2)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVALISYDGSQKYYADSMKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGHTSGTKAYYFDS WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGTSSNIGAGYSVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDXA DYYCQSYDSSLSGWVFGGXTKLTVLGEQKLISEEDLSGSAA **[SEQ ID NO:7]**
IL-2 (1)	EVQLLESGGGLVQPGGSLRLSCAASGFTFGDYAMSWVRQAPGKGLEWVSSISSRGSYIYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKKKTGYYGLDAWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCSS YAGSNNLVFGGXTKLTXLGEQKLISXXDLSGSAA **[SEQ ID NO:8]**
IL-2 (2)	EVXXLESGGGLVQPGGSLRLSCAASGFTFGDYAMSWVRQAPGKGLEWVSSISSRGSYIYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKKKTGYYGLDAWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCSS YAGSNNLVFGGXXKLTVLGEQKLISEXXLSGSAA **[SEQ ID NO:9]**
IL-2 (3)	EVQLLESGGGLVQPGGSLRLSCAASGFTFGDYAMSWVRQAPGKGLEWVSSISSRGSYIYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKKKTGYYGLDAWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSXIGAGYDVHWYQQLPGTAPKLLIYGNSNRP **[SEQ ID NO:10]**
IL-3 (1)	EVQLLESGGGLVQPGGSLRLSCAASGFTFGRYTMHWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARHFFESSGGYFDYWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDXADYYCA AWDDSLNGWVFGGXXKLTVLGEQKLISXXXLSGXAA **[SEQ ID NO:11]**
IL-3 (2)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGGARYDYWGQGTL VTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCQSYD NILRGVVFGGGTKLTVLXEQKLISEXDLSGSAA **[SEQ ID NO:12]**
IL-3 (3)	EVXXXESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGRGEYTYYAGSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCATGATRFGYWGQGTL VTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYGVQWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSXSLAISGLRSEDEADYYCQSY DSSLSYSVFGGXTKLTVLGEQKLISXXDLSGSAA **[SEQ ID NO:13]**
IL-4 (1)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVSSLHGGGDTFYTDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASLYGSGSYYYYYYGM DVWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGNNSNTGNNAVNWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGSKSGTSASLAISGLRSE DEADYYCCSYAGSYIWVFGGXTKLTVLGEQKLISXEXLSGSAA **[SEQ ID NO:14]**
IL-4 (2)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVSGISWNGGKTHYVDSVKGQFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGYCSNGVCYT ILDYWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTINWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDE ADYYCQSYDSSLSGWVFGGXTKLXVLXEQKLISXXDLSGSAA **[SEQ ID NO:15]**
IL-5 (1)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISSRSNYIYYSDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNFRFFDKWGQGTLVT VSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGGSSXIGANPVSWYQQLPGTAPKLLIYGNSNRP **[SEQ ID NO:16]**

IL-5 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISSRSNYIYYSDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNFRFFDKWGQGTLVT VSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGGSSNIGANPVSWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSS LSGSVFGGXTKLTVLXEQKLISEXXLSGSAA **[SEQ ID NO:17]**

IL-5 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISSRSNYIYYSDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNFRFFDKWGQGTLVT VSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGGSSNIGANPVSWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSS LSGSVFGGXTKLTVLGEQKLISXEDLSGSAA **[SEQ ID NO:18]**

IL-6 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNRGSSLYYGMDV WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCAGSSSNIGSKSVHWYQQLPGTAPKLLIYRNNRRPSGVPDRFSGSXSGTSXSLAIXGLRSXDXAD YYCXXWDDRVNXXXFGGXTXLTVLXXQKLISXXXLSGSXXXPSSSXXLIXXGXXXXLX-XXLXFTGRXFXTX-LXXX **[SEQ ID NO:19]**

IL-6 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVSSITSSGDGTYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAGGIAAAYAFDIW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNVGSNYVYWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYY CQSYDSSRWVFGGXTKLTVLGEQXLISEEXLSGSAA **[SEQ ID NO:20]**

IL-7 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVSGITWNSGSIGYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGPSVAARRIGRHW YNWFDPWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVYWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGSKSGTSASLAISGLR SEXXADYYCQSYDSSLSGSVFGGXXKLXVLGEQKLISEXXLSGSAA **[SEQ ID NO:21]**

IL-7 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYNIHWVRQPPGKGLEWVSGVSWNGSRTHYADSVKGQFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPAMVRGVVLPN YYGLDVWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGHSNRPSGVPDRFSGSKSGTSASLAISGL RSEXXADYYCQSYDSSLSYPVFGGXTKLTVLGEQ **[SEQ ID NO:22]**

IL-8 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSLISWDGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDLYGMDVWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYDNNKRPSXVPDRFSGSKSGTSASLAISGLRSEDEADYYC AAWDDSLSGWVFGGXTKLTVLXEQKLISEXXLSGSAA **[SEQ ID NO:23]**

IL-8 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYEMNWVRQAPGKGLEWVSSISSSSSYIFYADSMKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNESVDPLGGQYFQH WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGSKSGTSASLAISGLRSEDEA DYYCSAWDDNLDGPVFGGXTKLTVLXEQKLISXXXLSGSAA **[SEQ ID NO:24]**

IL-9 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTTFGHWGQGTLVTVSSG GGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSGSNIGDNSVNWYQQLPGTAPKLLIYGNNNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCSSYTSSSVVF GGXTKLTVLXEQKLISEXDLSGSAA **[SEQ ID NO:25]**

IL-9 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSPGGSPYYFDYWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSVSNIGSNVVSWYQQLPGTAPKLLIYDNNKRPS **[SEQ ID NO:26]**

IL-9 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSPGGSPYYFDYWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSVSNIGSNVVSWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYC QSYDSSLGGWVFGGXTKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:27]**

IL-10 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFRSYVMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGKGRWAFDIWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNVGAGYDVHWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSXDXADYY CAAWDDSLSAHVVFGGXTKLTVLGEQKLISXXDLSGSAA **[SEQ ID NO:28]**

IL-10 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFRSYVMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGKGRWAFDIWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNVGAGYDVHWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYY CAAWDDSLSAHVVFGGXTKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:29]**

IL-10 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGKGRWAFDIWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYGVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDXADYYCA AWDDSLSGLVFGGXTKLTVLXEQKLISEXXLSGSAA **[SEQ ID NO:30]**

IL-11 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNFGMHWVRQAPGKGLEWVAFIRYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARHYYYSETSGHPGG FDPWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSYPVNWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDE ADYYCQXWGTGVFGGXTKLTVLGEQKLISXEXLSGSAA **[SEQ ID NO:31]**

IL-11 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARHYYDVSYRGQQDA FDIWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNLGSPYDVHWYQQLPGTAPKLLIYRNDQRASGVPDRFSGSXSGTSASLAISGLRSE DEADYYCAAWDDSLNAWVFGGXTKLTVLGEQKLISEXXLSGSAA **[SEQ ID NO:32]**

IL-11 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVAYISGISGYTNYADSVRGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSKDWVNGGEMDVW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYVVHWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADY YCAAWDDSLRGWVFGGXTKLTVLGEQKLISEEDLSGSAA **[SEQ ID NO:33]**

IL-12 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSAIGTGGGTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAFRAFDIWGQGTLV TVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSRSNIGNNFVSWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWD DSLSGPVFGGXTKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:34]**

IL-12 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGQFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGSRSSPDAFDIW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADY YCAAWDDRVNGRVFGGGTKLTVLGEQKLISEXXLSGSAA **[SEQ ID NO:35]**

IL-13 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSGSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSQGWWTYYYGMDV WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEAD YYCETWGQ **[SEQ ID NO:36]**

IL-13 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSGSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSQGWWTYYYGMDV WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDXAD YYCETXDSNTQIFGGXTKLTVLGEQKLISEEXLSGSAXAHHHHHH-SXRXPIXXIVSXITIHXXSFXNVVTGKXXALPXXXALQHIPXXXAXXXX **[SEQ ID NO:37]**

IL-13 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSGSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSQGWWTYYYGMDV WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEAD YYCETWDSNTQIFGGXTKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:38]**

VEGF (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSNEMSWIRQAPGKGLEWVSSISGSGGFTYYADSVKGRYTISRDNSKNTLYLQMNSLRAEDTAVYYCARETTVRGNAFDIWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGGSSNIGAGYDVHWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSXSGTSASLAISGLRSEDEADYYC AAWDDSLSVPMFGGXTKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:39]**

VEGF (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSVGGWYEGDNW FDPWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSXVPDRFSGSXSGTSASLAISGLRSE XEADYYCQSYDGSLSGSVFGGXTKLTVLGEXKLISEXXLSGSAA **[SEQ ID NO:40]**

TGF-β1 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMSWVRQAPGKGLEWVAVVSIDGGTTYYGDPVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTRGPTLTYYFDYWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCQ SYDSSLSGWVFGGXTKLXVLGEQKLISEEDLSGSAA **[SEQ ID NO:41]**

TGF-β1 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFGDYAMSWFRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDGNRPLDYWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYC AAWDDRLNGWVFGGGTKLXVLGEQKLISEXDLSGSAA **[SEQ ID NO:42]**

TGF-β1 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYIGWIRQAPGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARRSTPSSSWALPDFF DYWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGANYDVHWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSED XADYYCQSYDSSLSGWVFGGXTKLTVLGEQKLISXXXLSGSAA **[SEQ ID NO:43]**

TNF-α (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTRHLGSAMGYWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSXVPDRFSGSXSGTSASLAISGLRSEDEADYYCQ SYDSSLSGWVFGGXTKLTVLXEQKLISXXDLSGSAA **[SEQ ID NO:44]**

TNF-α (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGGWGPRSAFDIWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVTWYQQLPGTAPKLLIYGNTNRLSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCE AWDDKLFGPVFGGXTXLTVLXEQKLISEXXLSGSAA **[SEQ ID NO:45]**

TNF-α (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVSGVNWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASIRANYYYGMDV WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGGSSNIGSHPVNWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEAD YYCAAWDASLSGWVFGGGXKLTVLXEXKLISXXXLSGSAA **[SEQ ID NO:46]**

GM-CSF (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVGGMSAPVDYWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYDNNKRPSGVPDRXSGSKSGTSASLAISGLRSEDEADYYC AAWDDSLIGLVVFGGXTKLTVLGEQKLISEXXLSGSAA **[SEQ ID NO:47]**

GM-CSF (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVAVISYDGSNEDSADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGPSLRGVSDYWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYNDNQRPSXVPDRFSGSKSGTSASLAISGLRSEDEADYYC QTWGTGINVIFGGXTKLXVLGEQKLISXEDLSGSAA **[SEQ ID NO:48]**

GM-CSF (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVAVISYDGSNEDSADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGPSLRGVSDYWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYNDNQRPSGVPDRFSGSKSGTSASLAISGLRSEDXADYYC QTWGTGINVIFGGXTKLTVLGEXKLISEXXLSGSAA **[SEQ ID NO:49]**

TNF-β (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFAMHWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASRSTLYYYYGMDVW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSTSNIGNSHVYWYQQLPGTAPKLLIYGNSNRPSXVPDRFSGSXSGTSASLAISGLRSEDEADYY CSSXAGSNNLVFGGXTKLTVLGEQKLISXXDLSGSAA **[SEQ ID NO:50]**

TNF-β (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSPYYGMDVWGQGT LVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYRNDQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCSS YGGRDNVVFGGXTKLTVLXEQKLISXXXLSGSAA **[SEQ ID NO:51]**

IL-1ra (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFDTHWMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARHDYGDYRAFDIW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYVVHWYQQLPGTAPKLLIYGNNNRPSGVPDRFSGSKSGTSASLAISGLRSEDEAD YYCQSYDSSLSGVVFGGXTKLXVLXEQKLISXEDLSGSAA **[SEQ ID NO:52]**

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IL-1ra (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSKYAMTWVRQAPGKGLEWVSAISGSGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARLVRGLYYGMDVW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGNNAVNWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSXDEADYY CQTXGTGPVVFGGXTKLTVLGEQKLISXXXXSGSAA **[SEQ ID NO:53]**

IL-1ra (3) EVQLLESGGGLVQPGGSLRLSCAVSGFTFSSYSMNWVRQAPGKGLEWVAGIGGRGATTYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARLRVVPAARFDYWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYC QSYDSSLSGPPWVFGGXXKLXVLXEQKLISEEDLSGSAA **[SEQ ID NO:54]**

IL-16 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNHAMSWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAALVQGVKHAFE IWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTALKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEAD YYCASWDDRLSGLVFGGXTKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:55]**

IL-16 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNHAMSWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAALVQGVKHAFE IWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTALKLLIYRNNQRPSGVPDRFSGSXSGTSASLAISGLRSEXEAD YYCASWDDRLSGLVFGGXTKLTVLXEQKLISEEDLSGSAA **[SEQ ID NO:56]**

IL-18 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLRGGRFDPWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYVVHWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSXSGTSASLAISGLRSEDEADYY CSSXAGSKNLIFGGXTKLTVLGEQKLISXXXLSGSAA **[SEQ ID NO:57]**

IL-18 (2) EVQLLESGRGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVSAIGTGGDTYYADSVMGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSPRRGATAGTFDY WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNIVNWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADY YCXSYDNSLSGWVFGGXXKLXVLGEXKLISEXDLSGSAA **[SEQ ID NO:58]**

MCP-4 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVSGISWNGGKTHYVDSVKGQFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGGYSSGWAFDY WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGRSSNIESNTVNWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEAD YYCAAWDDRLNAVVFGGXTKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:59]**

IFN-γ (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGRTGHGWKYYF DLWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGNNAVNWYQQLPGTAPKLLIYGNSNRPSXVPDRFSGSXSGTSASLAISGLRSEDE ADYYCQXWGTGLGVFGGXTKLTVLGEXKLISEEXLSGSAA **[SEQ ID NO:60]**

IFN-γ (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSRHGFHWVRQGPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGNWYRAFDIWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGGSSHIGRNFISWYQQLPGTAPKLLIYAGNSRP **[SEQ ID NO:61]**

IL-1β (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSYISSSGSTIYYADSVKGRSTISRDNSKNTLYLQMNSLRAEDTAVYYCARVRQNSGSYAYWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGTSSNIGAPYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDXADYYCQ SYDSSLSAVVFGGXTKLTVLGEQKLISEXXLSGSAA **[SEQ ID NO:62]**

IL-1β (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSRYVMTWVRQAPGKGLEWVSLISGGGSATYYADSMKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKRVPYDSSGYYPDAF DIWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDQFSGSKSGTSASLAISGLRSED EADYYCAAWDDSLNGPVFGGXTXLTXLXEQKLISEEXLSGSAA **[SEQ ID NO:63]**

IL-1β (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAVVSYDGNNKYYADSRKGRFTISRDNSKNTLYLQMNSLRAEDTAMYYCASYWYTSGWYPYG MDVWGQGTLGTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDLHWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRS EDEADYYCSSYVDNNNLVFGGXTKLTVLXEQKLISEXXLSGSAA **[SEQ ID NO:64]**

Eotaxin (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGKGTIAMPGRAR VGWWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGNNAVNWYQQLPGTAPKLLIYANSNRPSGVPDRFSGSXSGTSASLAISGLRSE DEADYYCAAWDDSLSGPVFGGXTKLTVLGEQKLISXXDLSXSAA **[SEQ ID NO:65]**

Eotaxin (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYWMTWVRQAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARQTQQEYFDYWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCFGSNSNIGSSTVNWYQQLPGTAPKLLIYDNDKRPSGVPDRFSGSXSGTSASLAISGLRSEDEADYYCAA WDDSLNGPVFGGXTKLTVLGEQKLISXXXLSGSXAAHHHHHH-SPRXPIRPIVSXXTIHWPSFYNVXTGKXXXLPNXIXXXHIPLSPAXXIXXXPXXXXX **[SEQ ID NO:66]**

Eotaxin (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFRGYAMSWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAPAVAGWFDPW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSHTVNWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDXADYY CAAWDDSLSGRVXGGGXKLTVLGEQKLISEEDLSGSAA **[SEQ ID NO:67]**

RANTES (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISNDGTKKDYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDASGYDDYYFDY WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGSDVHWYQQLPGTAPKLLIYRDDQRSSGVPDRFSGSKSGTSAFLAISGLRSEDEA DYYCQSYDNSLSGWVFGGXTKLTVLGEQKLISEXXLSGSAA **[SEQ ID NO:68]**

RANTES (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDNDYSSDTFDYWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSAFGTPGQRVTISCSGSSSNIGSDYVYWYQQLPGTAPKLLIYSDNQRP **[SEQ ID NO:69]**

RANTES (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGMNWVRQAPGKGLEWVSGVSWNGSRTHYVDSVKRRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARPRLRSHNYYGM DVWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSFKSGKNYVSWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDE ADYYCAAWDVRVKGVIFGGXTKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:70]**

MCP-1 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGGHQQLGQWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYRDSRRPSGVPDRFSGSKSGTSASLAISGLRSEXEADYYCA AWDDSLKGWLFGGXTKLTVLXEQKLISEXXLSGSAA **[SEQ ID NO:71]**

MCP-1 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSYISSSSSYTNYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARFRYNSGKMFDYWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGRNTVNWYQQLPGTAPKLLIYGNSNRRSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCA AWDDSLSGVVFGGXTKLTVLXEQKLISEXDLSGSAA **[SEQ ID NO:72]**

MCP-1 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSHYYDTTSFDYWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGTNPVNWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGSKSGTSASLAISGLRSEDXADYYC AAWDDSLSGVVFGGXTKLTVLGEQKLISXEDLSGSAA **[SEQ ID NO:73]**

MCP-3 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYGMHWVRQAPGKGLEWVSGVSWNGSRTHYVNSVKRRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVAPGSGKRLRAF DIWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGNNAVNWYQQLPGTAPKLLIYEVSKRPPGVPDRFSGSKSGTSASLAISGLRSEDXA DYYCSSYAGSSKWVFGGXTKLTVLGEQKLISEEDLSGSAA **[SEQ ID NO:74]**

MCP-3 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTLSSNYMSWVRQAPGKGLEWVSGISASGHSTHYADSGKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGKSLAYWGQGTLV TVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGNNAVNWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWD DSLSVVVFGGXTKLTVLGEQKLISXXXLSGSAA **[SEQ ID NO:75]**

MCP-3 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSIYWMSWVRQAPGKGLEWVAYIGGISNTVSYSDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKAPGYSSGWGWFDP WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGTNSVFWYQQLPGTAPKLLIYGNNNRPSGVPDRFSGSKSGTSASLAISGLRSEDXAD YYCMIWHSSASVFGXXTKLTVLGEQKLISEXXLSGSAA **[SEQ ID NO:76]**

β-gal EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVIAYDGINEYYGDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGGIYHGFDIWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYDNHKRPSGVPDRFSGSXSGTSASLAISGLRSEDEADYYCAA WDDNSWVFGGXTKLTVLGXYKDDDDKAA **[SEQ ID NO:77]**

Angiomotin (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDHYMDWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDTWAYGAFDIW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSNSNIGRNTVNWYQQLPGTAPKLLIYRDNQRPSGVPDRFSGSXSGTPASLAISGLRSEDXADY YCAAWDVSLNGWVFGGXTKLTVLGDYXDHDGDYKDHDIDXXDDDDXXAAHHHHHH-SPRWXIRPIVSRITIXWXXFYXVXXXKXX **[SEQ ID NO:78]**

Angiomotin (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFNDYYMTWIRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARERLPDVFDVWGQGTL VTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSGSNIGTNSVSWYQQLPGTAPKLLIYFDDLLPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWD DSLSGVVFGGXTKLTVLGXYKDHDGDYKDHDIDYKDDDXKAXAHHHHHH-SPRXXXRXIVSXIXIHXXXFYNXXTGKTXXXXXXIXXAAXXXFXX **[SEQ ID NO:79]**

Leptin EVQLLESGGGLVQPGGSLRLSCAASGFTFGDFAMSWVRQAPGKGLEWVANIKQDGSVKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARFLAGFYYGMDVW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSDSNIGGNTVNWYQQLPGMAPKLLIYYDDLLPSGVPDRFSGSKSGTSASLAISGLRSEDEADY YCAAYDDTMNGWGFGGXTKLTVLGXYKDXDDKAA **[SEQ ID NO:80]**

Integrin α-10 EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYNMNWVRQAPGKGLEWVSTISGSGGRTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRVATLDAFDIWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCA AWDDSLSGVVFGGXTKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:81]**

Integrin α-11 EVQLLESGGGLVQPGGSLRLSCAASGFTFRRDWMSWVRQVPGKGLEWVSVISGSDGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASYSPLGNWFDSWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYSDTYRPSGVPDRFSGSXSGTSASLAISGLRSEDEADYYC QSYDSSLXGFVVFGGXTKLTVLXEQKLISEXXLSGSAA **[SEQ ID NO:82]**

IgM (1) *EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSAIGSGPYYAHSVRDRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGGVEASFDYWGQGTLVT* VSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNTNRPSGVPNRFSGSKSGTSASLAISGLRSEDEADYYCQSYDN DLSGWVFGGXTKLXVLGEQKLISXXXLSGSAA **[SEQ ID NO:83]**

LDL (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAARYSYYYYGMD VWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGNNAVNWYQQLPGTAPKLLIYGNDRRPSGVPDRFSGSKSGTSASLAISGLRSEDEA DYYCQTWGTGRGVFGGGTKLTVLGEQKLISEXXLSGSAA **[SEQ ID NO:84]**

LDL (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVSSISTSSNYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVKKYSSGWYSNYAF DIWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSSIGNNFVSWYQQLPGTAPKLLIYDNNKRPSXVPDRFSGSXSGTSASLAISGLRSEDXA DYYCAAWDDSLNGWVFGGXTKLTVLXXYKDHDGDYXDHDIDYKDXXDKAA **[SEQ ID NO:85]**

PSA EVQLLESGGGLVQPGGSLRLSCAASGFTFRSYEMNWVRQAPGKGLEWVAVIGGNGVDTDYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVREEVDFWSGYYSY GMDVWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGDNFVSWYQQLPGTAPKLLIYRTNGRPSGVPDRFSGSXSGTSASLAISGLRSE DEADYYCATWDDNLNGRVVFGGXTKLTVLGDYKDXXDKAA **[SEQ ID NO:86]**

Lewis^{x} (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYWMHWVRQAPGKGLEWVANIKEDGSEKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGETSFGLDVWG *QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYC* ASWDDSLSGWVFGGXTKLTVLGDYKDDDDKAA **[SEQ ID NO:87]**

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Lewis^x (2)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSRYWMHWVRQAPGKGLEWVANIKPDGSEQYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGLSSGWSYGMD VWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSNSNIGSNTVNWYQQLPGTAPKLLIYTNINRPSGVPDRFSGSKSGTSASLAISGLRSXDEA DYYCATWDDSLSGWVFGGXTKLTVLGXYKDXXDKAA **[SEQ ID NO:88]**
Lewis^y	EVQLLESGGGLVQSGGSLRLSCAASGFTFSSYTLHWVRQAPGKGLEYVSAISSNGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASDVYGDYPRGLDYWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGTTSNIGSNYVHWYQQLPGTAPKLLIYGNNNRPSGVPDRFSGSKSGTSASLAISGLRSEDXADYYCQ SYDRSLGGLRVFGGXTKLTVLXDYKXDDDKAA **[SEQ ID NO:89]**
Sialle x	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMSWVRQAPGKGLEWVSSISSGNSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGRGRGGGFELWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGTYTVNWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSEXEADYYCSSN AGIDNILFGGXTKLTVLGEQKLISEXDLSGSXAAHHHHXXXXXXXXIXXXXXXXXXXXXXXXXXXLXX **[SEQ ID NO:90]**
TM peptide	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGFHWVRQAPGKGLEWVSLISWDGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGTWFDPWGQGTLV TVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIGNNAVNWYQQLPGTAPKLLIYRNNQRPSXVPDRFSGXXSGTSASLAIXGLRSEDEADYYCAAWD DSLSWVFGGXTKLTVLGDXXTMXVIIKIMTSXXXMTMXRRP **[SEQ ID NO:91]**
Procathepsin W	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSMSASGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGSYGMDVWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSTSNIGSYAVNWYQQLPGTAPKLLIYGNNNRPSGVPDRFSGSXSGTSASLAISGPRSEDEADYYC AAWDDSLNGGVFGGXTKLTVLGXYKXDDDKAA **[SEQ ID NO:92]**
BTK (1)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHLKRYSGSSYLFD YWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIGSNYVYWYQQLPGTAPKLLIY **[SEQ ID NO:93]**
Digoxin	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVAVIWHDGSSKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARATGDGFDYWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAA WDDSLNGVVFGGXTKLTVLGEQKLISXXXLSXSAA **[SEQ ID NO:94]**
GLP-1 R	EVQLLESGGGLVQPGGSLRLSCAASGFTFRSYGMHWVRQAPGKGLEWVSGLSWNSAGTGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKEMGNNWDHIDY WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEA DYYCAAWDDGLSGPVFGGGTKLTXLGEQKLISEEDLSGSAA **[SEQ ID NO:95]**
GLP-1	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYGMHWVRQAPGKGLEWVSAISGSGGSTYYAESVKGRSTISRDNSKNTLYLQMNSLRAEDTAVYYCVTRNAVFGFDVWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGFDVHWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYC QSFDSSLSGVVFGGXTKLTVLXEQKLISXEXLSGSAA **[SEQ ID NO:96]**
C1q	EVQLLESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQVPGKGLEWVSAISGSGATTFYAHSVQGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGGRGYDWPSGAF DIWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYENNKRPSXVPDRFSGSKSGTSASLAISGLRSEDX ADYYCAAWDDSVNGYVVFGGXTKLTVLGEQKLISEXXLSGSAAXXHHHHH-SPRWPIRPIXSRXTIXXPSFYXXXXXXTXXLPXXIXXXHXPXXXXXX **[SEQ ID NO:97]**
C1s	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARHMKAAAYVFEIW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSTAVNWYQQLPGTAPKLLIYSNNKRPSGVPDRFSGSXSGTSASLAISGLRSEDEADYY CAAWDDRLNGNVLFGGXXKLTVLXEQXLISXXXLSGSAA **[SEQ ID NO:98]**
C3 (1)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSVTGSGGGTYYADSVEGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYRWFGNDAFDIW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSASNLGMHFVSWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADY YCAAWDDTLNIWVFGGXTKLTVLGEQKLISXXXLSGSAA **[SEQ ID NO:99]**

C3 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYRMIWVRQAPGKGLEWVSSISGSNTYIHYADSVRGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRHPLLPSGMDVWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGKHPVNWYQQLPGTAPKLLIYRNDQRPSGVPDRFSGSKSGTSASLAISGLRSEDXADYYC QSYDSSLSGSWVFGGXTKLTVLGXQKLISEEDLSGSAA **[SEQ ID NO:100]**

C4 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYPMSWVRQAPGKGLEWVSTLYAGGWTSYADSVWGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARPKVESLSRYGMDV WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYVVHWYQQLPGTAPKLLIYDNSKRPSGVPDRFSGSKSGTSASLAISGLRSEDEA DYYCQSYDSSLSGVVFGGXTKLTVLXEQKLISEXXLSGSAA **[SEQ ID NO:101]**

C5 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYRMNWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGGGWFSGHYYFDY WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGATSNIGAGYDVHWYQQLPGTAPKLLIYRNNQRPSXVPDRFSGSXSGTSASLAIXGLRSEDXA DYYCQSYDSSLRHWVFXGXXKLTVLXEQKLISEXXLSGSXA **[SEQ ID NO:102]**

C5 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYSMNWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARENSGFFDYWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGSNTVNWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLTISGLRSEDXADYYCA AWDDSLSGWVFGGXTKLTVLXEQKLISEEXLSGSAA **[SEQ ID NO:103]**

C1 inh (1) EVQLLESGGGLVQPGGSLXLSCAASGFTFSDYYMSWIRQAPGKGLEWVSGISRGGEYTFYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPGGLDAFDIWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGARYDVQWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEXXADYYCAS WDDSLSGPVFGGXTKLTVLXEQKLISEXXLSXSAA **[SEQ ID NO:104]**

Factor B (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVAVISYDGRFIYYSDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSYGGNLAMDVWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGSNSGTSASLAISGLRSEDXADYYC AAWDDRLNGRVVFGGXTKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:105]**

IL-12 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGLEWVASIRGNARGSFYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGDSSGWYFFDYW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSDSXIGAGFDVHWYQQLPGTAPKLLIYGNNNRPSGVPDRFSGSKSGTSASLAISGLRSEDXAD YYCQSYDTSLSGVLFGGXXKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:106]**

IL-12 (4) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVSTVSGSGDNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTTTWRYWGQGTLVT VSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSSL SGWVFGGXTKLTVLXEQKLISXEDLSGSAA **[SEQ ID NO:107]**

IL-16 (3) EVXLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARERGDAFDIWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSDNQRPSGVPDRFSGSKSGTSASLAISGLRSXXEADYYCAA WXDSLNGPWVFGGXTKLXVLGEQKLISEEDLSGSAA **[SEQ ID NO:108]**

IL-18 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARHGYGDSRSAFDIW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSXSGTSASLAISGLRSEXXADY YCQSYDSSLSRWVFGGXTKLXVLGEQKLISXXXLSXSAA **[SEQ ID NO:109]**

IL-1a (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSYISSSSSYTNYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSVTRRAGYYYYYSGM DVWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIGSNTVNWYQQLPGTAPKLLIYRNNQRPSXVPDRFSGSXSGTSASLAISGLRSEDE AXYYCSSXAGSNSXVFGGXTKLTVLGEQKLISXXXLSGSAA **[SEQ ID NO:110]**

IL-6 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVSSITSSGDGTYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAGGIAAAYAFDIW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNVGSNYVYWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGSKSGTSASLAISGLRSEXEADYY CQSYDSSRWVFGGXTKLTVLGEQKLISEXXLSGSAA **[SEQ ID NO:111]**

IL-6 (4) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSNYMSWVRQAPGKGLEWVSSISSSSTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARQPASGTYDAFDIWGQG
TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSXSGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYYDDLLPSGVPDRFSGSKSGTSASLAISXLRSEDEADYYCAV
WDDSLSGWVFGGXTKLTVLXEQKLISXXDLSGSAXAHHHHHHXSPRXXIRPIVSXITIHXXVVLXRRDWEXPXXTQLNXXXAHXPFXXXXNX **[SEQ ID NO:112]**

IL-8 (3) EVQXLESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSLISWDGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDLYGMDVWGQ
GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGSKSGTSASLAISGLRSXDEADYYC
AAWDDSLSGWVFGGXTKLTVLGEQKLISEXXLSGSAA **[SEQ ID NO:113]**

MCP-4 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVSGISWNGGKTHYVDSVKGQFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGGYSSGWAFDY
WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGRSSNIESNTVNWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSEXEADY
YCAAWDDRLNAVVFGGXTKLXVLXEQKLISEXXLSGSAA **[SEQ ID NO:114]**

Properdin EVQLLESGGGLVQPGGSLRLSCAASGFTFSSNYMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGGSGWYDYFDYWG
QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEAXYY
CAAXDDGLNSPVFGGGTKLXVLXEQKLISEEDLSGSAXAHHHHHH-SPRXXIRPIVSRITIHWXXFXXXXXGKTXXXPXLXXXXXXPPFX **[SEQ ID NO:115]**

TNF-β (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSGLSGSAGRTHYADSVRGRFTISRDNSKNTLYLQMNSLRAEDTAMYYCASSLFDYWGQGTLVT
VSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDXADYYCAAWDDS
LNAVVFGGXTKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:116]**

TNF-β (4) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMNWVRQAPGKGLEWVSGINWNSDDIDYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAMYYCAIDSRYSSGWSFEY
WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSTSNIGNSHVYWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEAD
YYCQSYDSSLSGVVFGGXTKLTVLGEQKLISXXXLSGSAA **[SEQ ID NO:117]**

VEGF (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYEMNWVRQAPGKGLEWVSGISGSGGFTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAMYYCAREGYQDAFDIWGQ
GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYSNNQRPSXVPDRFSGSXSGTSASLAISGLRSEDXADYYC
AAWDDSLSGPPWVFGGGXKLXVLXEQKLISXXXLSGSXAAHHHHHH-SPRXPIRPIVSXIXIHWPXFYNVXXXXTXXXPXLX **[SEQ ID NO:118]**

VEGF (4) EVQLLESGGGLVQPGGSLRLSCAASGFTFXXXYXSWVRQAPGKGLEWVSXISWXXGSIGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCXXXXXXXXNYFDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSNSNIGGNFVYWYQQLPGTAPKLLIYENSKRPSXVPDRFSGSXSGTSASLAISGLRSEDXADYYCAA
WDDSLXXVVFGGXTKLTVLGEQKLISXXXLSGSAA **[SEQ ID NO:119]**

IL-4 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAIAARPFDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGATSNIGAGYDIHWYQQLPGTAPKLLIYSTNNRPSGVPDRFSGSKSGTSASLAISGLRSEDXADYYCA
AWDDSLNGPVFGGXXKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:120]**

CD40 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYWMHWVRQAPGKGLEWVSGISGGGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARMTPWYYGMDV
WGQGTLVTVSSGGGGSGGGGSGGGGSQSMLTQPPSASGTPGQRVTISCSGSTS **[SEQ ID NO:121]**

CD40 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYGMHWVRQAPGKGLEWLSYISGGSSYIFYADSVRGRFTISRDNSENALYLQMNSLRAEDTAVYYCARILRGGSGMDLWGQG
TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPXXSGTPGQRVTISC **[SEQ ID NO:122]**

CD40 (4) EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYGMHWVRQAPGKGLEWLSYISGGSSYIFYADSVRGRFTISRDNSENALYLQMNSLRAEDTAVYYCARILRGGSGMDLWGQG
TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVYWYQQLPGTAPKLLIYGNINRPSGVPDRFSGSKSGTSASLAISGLRSEDXADYYCAA
WDDSLXGLVFGGXXKLTVLXXYKDDDDKAA **[SEQ ID NO:123]**

CT17 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSSAMHWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVKGRVTIFGVVINSN
YGMDVWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSISSIGSNAVSWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSE
DXADYYCAAWDDSLNGHDVVFGGXTKLTVLXDYKDXDXKAA **[SEQ ID NO:124]**

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IgM (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGDYSSSPGGYYYYM DVWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIGSNTVNWYQQLPGTAPKLLIYGNSNRPSXVPDRFSGXXSGTSASLAIXGLRSXDX ADYYCSSXXSTNTVIFGGXTKLTVLGEQKLISXXDLSGSAA **[SEQ ID NO:125]**

IgM (4) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSNEMSWIRQAPGKGLEWVSAIYSGGGTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVNDYGDNVYFDHWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYENNKRPSXVPDRFSGSXSGTSASLAISGLRSEDEADYYCA AWDDSLSVYVVFGGXTKLXVLGEQKLISXXDLSGSAA **[SEQ ID NO:126]**

IgM (5) EVQLLESGGGLVQPGGSLRLSCAASGFTFGSYEMNWVRQAPGKGLEWVSVIYSGGSTYYADSVEGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDTNPYYYYGMDVW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGNNAVNWYQQLPGTAPKLLIYRNNQRPSXVPDRFSGSXSGTSASLAISGLRSEDEADYY CQSYDSSLNGQVFGGXTKLTVLXEQKLISXEXLSGSAA **[SEQ ID NO:127]**

HLA-DR/DP EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDGLLPLDYWGQGTL VTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGGSSNIGGNAVNWYQQLPGTAPKLLIYENNKRPSXVPDRFSGSXSGTSASLAISGLRSEDXADYYCSSYA VSNNFEVLFGGXTKLTVLXEQKLISXXDLSGSAA **[SEQ ID NO:128]**

ICAM-1 EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVAFIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYSGWYFDYWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSXIGAGYDVHWYQQLPGTAPKLLIYDNNNRPSXVPDRFSGSXSGTSASLAISGLRSEDEADYYC QSYDSSLSAWLFGGXTKLTVLGEQKLISXXDLSGSXAAHHHHHH-SPRWPIRXIVSXXTIXXPXFYXVXXXKPXXTXLXRXXAHPXX **[SEQ ID NO:129]**

IgM (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSAIGSGPYYAHSVRDRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGGVEASFDYWGQGTLVT VSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNTNRPSXVPNRFSGSXSGTSASLAISGLRSEDEADYYCQSYDN DLSGWVFGGXTKLTVLGEQKLISEEXLSGSAA **[SEQ ID NO:130]**

MCP-1 (4) QSVLTQPPSASGTPGQRVTISCTGSSSNIGSDYGVQWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLSGPVFGGGTKLTVLG **[SEQ ID NO:131]**

MCP-1 (5) QSVLTQPASASGTPGQRVTISCTGNSSNIGAGYDVHWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLLSEDEADYYCAAWDYSLNGWVFGGGTKLTVLG **[SEQ ID NO:132]**

MCP-1 (6) QSVLTQPSSASGTPGQRVTISCTGNSSNIGAGYDVHWYQQLPGTAPNLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGWVFGGGTKLTVLG Q **[SEQ ID NO:133]**

MCP-1 (7) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVAYINRGSTYTNYADSMKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARRGYGSGSYYAFDI WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGSDYGVQWYQQLPGTAPKLLIYSNNQRPSXVPDRFSGSKSGTSASLAISGLRSEDXA DYYCAAWDDSLSGPVFGGX **[SEQ ID NO:134]**

MCP-1 (8) EVQLLESGGGLVQPGGSLRLSCAASGFTFGDYAMSWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPDPSGTDAFDFW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSXVPDRFSGSXSGTSASLAISGLRSEDXADY YCAAWDDSLSAWAFGG **[SEQ ID NO:135]**

MCP-1 (9) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYEMNWVRQAPGKGLEWVSAISGPGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLSDYGDFDYWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDAHWYQQLPGTAPKLLIYDNNKRPXXVPDRFSGSXSGTSASLAISGLRSEDEADYYC ATWDDSLRGWVFG **[SEQ ID NO:136]**

Cystatin C (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVGLISYDGRTTYYADSVKGRSTISRDNSKNTLYLQMNSLRAEDTAVYYCATTTGTTLDYWGQGTL VTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNTNRPSXVPDRFSGSXSGTSASLAISGLRSEDEADYYCAA WDDSLYGWVFGGXTKLTVLGDYXDHDGDYXDHDIDXXDDDDKAA **[SEQ ID NO:137]**

Cystatin C (2)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVAFISYDGSNKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDGVPAVPFDYWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGAGYDVHWYQQLPGTAPKLLIYSNNQRPS **[SEQ ID NO:138]**
Cystatin C (3)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMTWVRQAPGKGLEWVADISHDGFHKYYADSVRGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYGRVLPYYYYYGM DVWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPRQRVTISCTGSSSXIGAGYDVHWYQQLPGTAPKLLIYGNSNRP **[SEQ ID NO:139]**
Cystatin C (4)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVGLISYDGRTTYYADSVKGRSTISRDNSKNTLYLQMNSLRAEDTAVYYCATTTGTTLDYWGQGTL VTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNTNRPSXVPDRFSGSXSGTSXSLAISGLRSXDEADYYCAA WDDSLYGWVFGG **[SEQ ID NO:140]**
Apo-A1 (1)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNNGMHWVRQAPGKGLEWVSAISASGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCATHGGSSYDAFDIWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYVVHWYQQLPGTAPKLLIYG **[SEQ ID NO:141]**
Apo-A1 (2)	EVQLLESGGGLVQPGGSLRLSCAASGFTFRDYYMSWIRQAPGKGLEWVAVTSYDGSKKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDYADDSIAAPAFDI WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSXIGAGYDVHWYQQLPGTAPKLLIYGNSNRPS **[SEQ ID NO:142]**
Apo-A1 (3)	EVXXLESGGGLVQPGGSLRLSCAASGFTFRDYYMSWIRQAPGKGLEWVAVTSYDGSKKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDYADDSIAAPAFDI WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSXDEA XYYCQSYDSSLSVVFGGGTKLTVLXXYXDHDGDYKDHDIDYXDDXXXAXAHHHHHH-SPXXXIRXXXSXXTIHXXXXXXXXDWXXXXXXXXX **[SEQ ID NO:143]**
Factor B (2)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVAVISYDGRFIYYSDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSYGGNLAMDVWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGSNSGTSASLAISGLRSEDEADYYC AAWDDRLNGRVVFGGXTKLTVLGDYXDHDGDYKDHDIDXKDDDXKAA **[SEQ ID NO:144]**
Factor B (3)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVAVISYDGSNQYYADSVRGRFTISKDNSKNTLYLQMNSLRAEDTAVYYCAREWHYSLDVWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIGSNTVNWYQQLPGTAPKLLIYRNNQRPSXVPDRFSGSXSGTSASLAIXGLRSEDXADYYCAA WDD **[SEQ ID NO:145]**
Factor B (4)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSKHSMNWVRQAPGKGLEWVATVSYDGNYKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGYYYYGMDVWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGNNAVNWYQQLPGTAPKLLIYNNNQRPXXVPDRFSGSXSGTSXSLAISGLRSEDEADYY CQPYXDXLSSVVFGGXTXLTVLXDXXDHDXXYKDHDIXYXDXDXXXXAHHHHHH-SPRWPIRPIVSXIXIXWXXVLXRXXXXNXXXXXXXXXXXXHXXXXXX **[SEQ ID NO:146]**
C1 inh (2)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNRGNWGTYYFDY WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVSWYQQLPGTAPKLLIYGSSNRPSGVPDRFSGSXSGTSASLAISGLRSEDEADY YCQSYDSSLSDHVVFGGXTKLTVLXDYXDHDGDYKDHDIDXXDDDDXAA **[SEQ ID NO:147]**
C1 inh (3)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNRGNWGTYYFDY WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIGSNYVSWYQQLPGTAPKLLIYGSSNRPSXVPDRFSGSXSGTSASLAISGLRSEDXADYY CQSYDSSLSDHVVFGGXTKLTVLGDYXDHDGDYKDHDXDXXDDXXXAA **[SEQ ID NO:148]**
C1 inh (4)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNRGNWGTYYFDY WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIGSNYVSWYQQLPGTAPKLLIYGSSNRPSXVPDRFSGXXSGTSASLAISGLRSEDEADY YCQSYDSSLSXHVVFGGXTKLTVL **[SEQ ID NO:149]**
C5 (3)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCLTLGGYWGQGTLVTVSS GGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSXDEADYYCQSYDSSLSG WVFGGXTKLTVLXDYKXHDGDYKDHDIDXKDDDXXAA **[SEQ ID NO:150]**

C4 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGYGSGSRATGYNW FAPWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSXSGTSXSLAISGLRSE DXADYYCQSYDSSLXGPYWVFXXXNQXDGPRXXXKTMTXXXXXXDIDYXXXXXQXRXAXXXHHH-SPXXP **[SEQ ID NO:151]**

C4 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGWSTSSFDYWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIGNHYVSWYQQLPGTATKLLIYXDDLLPSXVPDRFSGSXSGTSASLAIXGLRSEDEADYYCAAW DDRSGQVLFGGXTKLTVLGDYXDHDGDYXDHDIDXXDDDXKAXAHHHHHH-XXRWPIRPXVSXXTIHXXXFXXXXXXKT **[SEQ ID NO:152]**

C4 (4) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSGISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHSGYGFDIWGQGTL VTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGGASXLGMHFVSWYQQLPGTAPKLLIYYDDLLPSGVPDRFSGXXSGTSASLAISGLRSEDEADYYCAAW DDSLNGWVFGGXTKLXVLGDYXDXXGDYKDHDIDXKDXXXXAXAHXHHHH-SPXWXXRPIVXXITXXXXVXLQRXDWXXPXVXXXXXXXXXXPX **[SEQ ID NO:153]**

C3 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVANINQDGSTKFYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDTGGNYLGGYYYY GMDVWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYRNDQRPSXVPDRFSGSXSGTSASLAISGLRSX DXADYYCSSYAGNNNLVFGGXTKLTVLGDYXDHDGDYKDHDIDYXDXDXXAA **[SEQ ID NO:154]**

C3 (4) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDHYMDWVRQAPGKGLEWVSGISGNGATIDYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARPSITAAGSEDAFDL WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLRSXDGAD YYCQSYDSSLSGWVFGGXTKLTVLGXYXDHDGDYKDXDIDYKDDXXKAA **[SEQ ID NO:155]**

C3 (5) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYWMSWVRQAPGKGLEWVSGISGSGGTTYYADFVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARKYYYGSSGAFDIW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYRNNQRPSXVPDRFSGSXSGTSASLAIXGLRSEDXAD YYCAAWDDSLXGPVFXGXTKLTVL **[SEQ ID NO:156]**

C3 (6) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVANINQDGSTKFYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDTGGNYLGGYYYY GMDVWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYRNDQRPSGVPDRFSGSXSGTSASLAISGLRSE DXADYYCSSYAGNNNLVFGGXXKLTVLGXXXDHDGDYKDHDIDXXDXDXXAA **[SEQ ID NO:157]**

MYOM2 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSGISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGVVAGSWGQGTLV TVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIGNNAVNWYQQLPGTAPKLLIYDNNKRPSXVPDRFSGXXSGTSXSLAIXGLRSEDEADYYCA **[SEQ ID NO:158]**

MYOM2 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNEWMAWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGTYHDFWSATYWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYGNSNRPSXVPDRFSGSXSGTSASLAISGLRSEDXADYYCAA WDDSLNGWVFGGXTKLTVLGD **[SEQ ID NO:159]**

LUM EVQLLESGGGLVQPGGSLRLSCAASGFTFSSNYMSWVRQAPGKGLEWVSAISASGTYTYYTDSVNGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVNTVGLGTPFDNW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYGNRNRPSGVPDRFSGSXSGTSASLAISGLRSEDEADYY CAAWDDSLSGWVFGGXTKLTVLXDYXDHDGDYKDHDIDXXXDDXXAA **[SEQ ID NO:160]**

DUSP9 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGFHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGEFGVYWGQGTLV TVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYGNRNRPSGVPDRFSGSXSGTSASLAISGLRSEDEADYYCSSYAGS NNFEVVFGGXTKLTVLGDYXDHDGDYKDHDIDYKDDDXKAA **[SEQ ID NO:161]**

CHX10 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNSDYYGMDVWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGYSDVYWYQQLPGTAPKLLIYENNKRPSXVPDRFSGSXSGTSASLAISGLRSEDEADYYCST WDDSLNGHVIFGG **[SEQ ID NO:162]**

CHX10 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNYGDSINWFDPWG QGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIRSNTVNWYQQLPGTAPKLLIYGNSNRPSXVPDRFSGXXSGTSXSLAISGLRSEDXADYYCA XWDDSLN **[SEQ ID NO:163]**

ATP-5B (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSKTYHADSVEGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARHLRPYYFDYWGQG TLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIGSNTVNWYQQLPGTAPKLLIYGNSNRPSXVPDRFSGXXSGTSASLAISGLRSEDXADYYCSA WDDRLRGRVFGG **[SEQ ID NO:164]**

ATP-5B (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVSLISSASSYIYHADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAGRVCTNGVCHTTFD YWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGDRSNIGSNTVNWYQQLPGTAPKLLIYGNSNRPSGVPXRFSGSXSGTSXSLAISGLRSEDEA DYYCQSYDSSLSAVVFGGXTKLTVLGDYXXHDXXYKDHDIDYXXDXDXAXAHXHHHH-SPRXXXXPIVSXXXXXXXXXXXXXXXLXKXXXXPTXXXXXXXX **[SEQ ID NO:165]**

ATP-5B (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMSWVRQAPGKGLEWVSSISSTSTYIHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVSSWYSAFDIWGQGT LVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGNNAVNWYQQLPGTAPKLLIYSNNQRPSXVPDRFSGSXSGTSASLAISGLRSEDXADYYCQSY DSSLSGVIFGGXTKLXVLXDYXDHDGDYXDHDIDXXXDDDKAA **[SEQ ID NO:166]**

Sox11a EVQLLESGGGLVQPGGSLRLSCAASGFTFSDFWMSWVRQAPGKGLEWVSSISGGGGTAFYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTALYYCARMTDLESGDAFDIW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVNWYQQLPGTAPKLLIYNDNVRPSGVPDRFSGSXSGTSASLAISGLRSEDXADYY CQXWGTGVFGGXTKLTVLXDYXDHDGDXXDHDIDXKDXDXKAA **[SEQ ID NO:167]**

TBC1D9 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMSWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRTRGSTALDIWGQ GTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSYIGSNYVYWYQQLPGTAPKLLIYRNNQRPXXVPDRFSGXXSGTSASLAISGLRSEDEADYYCAA WDDSLSGWVFGGXTKLTVLGD **[SEQ ID NO:168]**

UPF3B (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWVSDISWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCSSHLVYWGQGTLVTV SSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYDNNKRPSXVPDRFSGSXSGTSASLAIXGLRSEXXADYYCQTYDSS LSGSVVFGGXTKLTVLGDYXDHDXDY **[SEQ ID NO:169]**

UPF3B (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSYISSSSSYANYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARLGVYSGTYLFAFDIW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSXIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSXVPDRFSGSXSGTSASLAISGLRSXDEADY YCQSRDSSLSGWVFGGXTKLTVLGD **[SEQ ID NO:170]**

Apo-A4 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVAYDIDAFDMW GQGTLVTVSSGGGG **[SEQ ID NO:171]**

Apo-A4 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWVRQAPGKGLEWVSGVSWNGSRTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVAYDIDAFDMW GQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSFSNIGSNYVYWYQQLPGTAPKLLIYENNKRPSGVPDRFSGSXSGTSASLAISGLRSEDEADYYC AAWDDSLNGPMFGGXTKLTVLXDYKDHDGDYKDHDIDYKDDXXXXAAHHHHHH-SPRWXIRPXXSXXTIHXXXXLXXXD **[SEQ ID NO:172]**

Apo-A4 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSAITGSGNATFYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTTGATTRWGQGTLVT VSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSRSNIGSNHVFWYQQLPGTAPKLLIYENNKRPSGVPDRFSGSXSGTSASLAISGLRSEDXADYYCAAWDD SLSGWVFGG **[SEQ ID NO:173]**

TBC1D9 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVSFISSSSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVNLVGCTNGVCNGH DYWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIGSNTVNWYQQLPGTAPKLLIYDNNKRP **[SEQ ID NO:174]**

TBC1D9 (3) EVQLLESGGGLVQPGGSLRLSCAASGFTFGDYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGRTMASHWGQGT LVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIGNNHVSWYQQLPGTAPKLLIYGNSNRPSXVPDRFSGSXSGTSASLAISGLRSEDXADYYCAAW DNSLKVWMFGG **[SEQ ID NO:175]**

ORP-3 (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSNYMSWVRQAPGKGLEWVSYISGNSGYTNYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARHAGSYDMYGMDV
WGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSTSXIGSHYVYWYQQLPGTAPKLLIYGNSNRPXXVPDRFSGXXSGTSXSLAISGLRSEDXADY
YCQSYDSRLSGWVFGG **[SEQ ID NO:176]**

ORP-3 (2) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARKSSLDVWGQGTLV
TVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCSGSSSXIGNNYVSWYQQLPGTAPKLLIYDDNKRPSGVPDRFSGSXSDTSASLAISGLRSEDEADYYCAAWDD
SLXGRVFGGXTKLTVLG **[SEQ ID NO:177]**

CIMS (5) EVXLLESGGGLVQPGGSLRLSCAASGFTFSDHYMDWVRQAPGKGLEWVSGISGSGGSTYYGDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASRLYWGQGTLVTVSS
GGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYVVHWYQQLPGTAPKLLIYDNDKRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSL
DAVLFGGXXKLTVLGEQKLISEXDLSGSAA **[SEQ ID NO:178]**

CIMS (13) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGRTYYTDSVRDRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLMPVCQYCYGMD
VWGQGTLVTVSSGGGGSGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSXSGTSASLAISGLRSEDE
ADYXCQSYDSSLNKDVVFGGXTKLTVLGEQKLISXXDLSGSAXAHHHHHH-SPRXPIRPIVSRXTIHWXXXLXXXDWENXXXTXLXXXAXXPPFXXXXX **[SEQ ID NO:179]**

* The structure of the scFv antibodies is described in Söderlind et al., 2000, 'Recombining germline-derived CDR sequences for creating diverse single-framework antibody libraries' *Nature Biotechnol.*, 18(8):852-6, which is incorporated herein by reference in its entirety.

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CLAIMS

1. A method for determining a systemic lupus erythematosus-associated disease state in a subject comprising the steps of:

    a) providing a sample to be tested; and
    b) measuring the presence and/or amount in the test sample of one or more biomarker(s) selected from the group defined in Table A;

wherein the presence and/or amount in the test sample of the one or more biomarker(s) selected from the group defined in Table A is indicative of the systemic lupus erythematosus-associated disease state in the subject.

2. The method according to Claim 1 further comprising the steps of:

    c) providing a control sample from an individual with a different systemic lupus erythematosus-associated disease state to the test subject; and
    d) measuring the presence and/or amount in the control sample of the one or more biomarkers measured in step (b);

wherein the systemic lupus erythematosus-associated disease state is identified in the event that the presence and/or amount in the test sample of the one or more biomarkers measured in step (b) is different from the presence and/or amount in the control sample.

3. The method according to Claim 1 or 2 further comprising or consisting of the steps of:

    e) providing a control sample from an individual with the same systemic lupus erythematosus-associated disease state to the test subject; and
    f) measuring the presence and/or amount in the control sample of the one or more biomarkers measured in step (b);

wherein the systemic lupus erythematosus-associated disease state is identified in the event that the expression in the test sample of the one or more biomarkers measured in step (b) corresponds to the expression in the control sample of the one or more biomarkers measured in step (f).

4. The method according to Claim 1, 2 or 3 wherein step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table A, for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68 or 69 of the biomarkers defined in Table A.

5. The method according to any one of Claims 1-4 wherein step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table A(I) and/or (II), for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 of the biomarkers defined in Table A(I) and/or (II).

6. The method according to any one of Claims 1-5 wherein step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table A(III), for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 21, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48 or 49 of the biomarkers defined in Table A(III).

7. The method according to any one of Claims 1-6 wherein step (b) comprises or consists of:

a) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(I), for example, 2 or 3 of the biomarkers defined in Table B(I);
b) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(II), for example, 2 or 3 of the biomarkers defined in Table B(II);
c) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(III), for example, 2 of the biomarkers defined in Table B(III);
d) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(IV), for example, 2 of the biomarkers defined in Table B(IV);
e) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(V), for example, 2, 3 or 4 of the biomarkers defined in Table B(V);

f) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(VI), for example, 2 of the biomarkers defined in Table BV(VI);

g) measuring the presence and/or amount in the test sample the biomarker defined in Table B(VII);

h) measuring the presence and/or amount in the test sample the biomarker defined in Table B(VIII);

i) measuring the presence and/or amount in the test sample the biomarker defined in Table B(IX);

j) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(X), for example, 2, 3, 4, 5, 6 or 7 of the biomarkers defined in Table B(X);

k) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(XI), for example, 2, 3, 4, 5, 6, 7 or 8 of the biomarkers defined in Table B(XI);

l) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(XII), for example, 2 or 3 of the biomarkers defined in Table B(XII);

m) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(XIII), for example, 2 of the biomarkers defined in Table B(XIII);

n) measuring the presence and/or amount in the test sample the biomarker defined in Table B(XIV);

o) measuring the presence and/or amount in the test sample the biomarker defined in Table B(XV);

p) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(XVI), for example, 2, 3, 4, 5, 6, 7 or 8 of the biomarkers defined in Table B(XVI);

q) measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(XVII), for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 of the biomarkers defined in Table B(XVII);

r) measuring the presence and/or amount in the test sample the biomarker defined in Table B(XVIII); and/or

s) measuring the presence and/or amount in the test sample the biomarker defined in Table B(XIX).

8. The method according to any one of Claims 1-7 wherein the method comprises, consists of, or is for determining whether the SLE-associated-disease state is active SLE or non-SLE.

9. The method according to Claim 8 wherein step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(I), (II), (III), (IV), (V), (VI), (VIII), (IX), (X), (XI), (XIV) and/or (XVI).

10. The method according to any one of Claims 1-6 wherein the method comprises, consists of, or is for determining whether the SLE-associated-disease state is non-active SLE or non-SLE.

11. The method according to Claim 10 wherein step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(I), (II), (III), (V), (VII), (IX), (X), (XII) and/or (XV).

12. The method according to any one of Claims 1-6 wherein the method comprises, consists of, or is for determining whether the SLE-associated-disease state is highly active SLE or non-SLE.

13. The method according to Claim 12 wherein step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(I), (II), (IV), (VI), (XII), (XIII), (XIV) and/or (XVIII).

14. The method according to any one of Claims 1-6 wherein the method comprises, consists of, or is for determining whether the SLE-associated-disease state is active SLE or non-active SLE.

15. The method according to Claim 14 wherein step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(I), (II), (III), (IV), (V), (VII), (VIII), (XI), (XV) and/or (XVII).

16. The method according to any one of Claims 1-6 wherein the method comprises, consists of, or is for determining whether the SLE-associated-disease state is highly active SLE or non-active SLE.

17. The method according to Claim 16 wherein step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers defined in Table B(I), (II), (IV), (VI), (XII), (XIII), (XIV) and/or (XVIII).

18. The method according to any one of the preceding claims wherein the method comprises or consists of measuring all of the biomarkers listed in Table A and Table B.

19. The method according to any one of Claims 2-18 wherein the control sample of step (c) or step (e) is provided from:

a) a healthy individual (non-SLE);
b) an individual with non-active SLE (non-flaring SLE);
c) an individual with active SLE (flaring SLE); or
d) an individual with highly-active SLE (strongly flaring SLE).

20. The method according to any one of Claims 2-18 or Claim 19(b), (c) or (d) wherein the control sample of step (c) or step (e) is provided from:

a) an individual with SLE subtype 1 (SLE1);
b) an individual with SLE subtype 2 (SLE2); or
c) an individual with SLE subtype 3 (SLE3).

21. The method according to any one of the preceding claims wherein the physical symptoms of the SLE-associated disease state are present.

22. The method according to any one of Claims 1-21 wherein the SLE-associated disease state is determined before the appearance of the physical symptoms of the SLE-associated disease state.

23. The method according to Claim 22 wherein the SLE-associated disease state is determined at least 1 day before the appearance of the physical symptoms of the SLE-associated disease state, for example, at least 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 13 months, 14, months, 15, months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22

months, 23 months or 24 months before the appearance of the physical symptoms of the SLE-associated disease state.

24. The method according to any one of the preceding claims wherein step (b) and/or step (d) is performed using a binding agent capable of binding to the one or more biomarker(s).

25. The method according to Claim 24 wherein the first binding agent is an antibody or a fragment thereof.

26. The method according to Claim 25 wherein the antibody or fragment thereof is a recombinant antibody or fragment thereof.

27. The method according to Claim 25 or 26 wherein the antibody or fragment thereof is selected from the group consisting of: scFv; Fab; a binding domain of an immunoglobulin molecule.

28. The method according to any one of the preceding claims wherein the one or more biomarker(s) in the test sample and/or one or more binding agent(s) are labelled with a detectable moiety.

29. The method according to Claim 27 or 28 wherein the detectable moiety is selected from the group consisting of: a fluorescent moiety, a luminescent moiety, a chemiluminescent moiety, a radioactive moiety, and an enzymatic moiety.

30. The method according to any one of the preceding claims wherein step (b), (d) and/or (f), where present, is performed using an array.

31. The method according to Claim 30 wherein the array is a bead-based array.

32. The method according to Claim 30 or 31 wherein the array is a surface-based array.

33. The method according to Claim 30, 31 or 32 wherein the array is selected from the group consisting of macroarray, microarray and nanoarray.

34. The method according to any one of Claims 1-29 wherein step (b), step (d) and/or step (f), where present, are performed using ELISA (Enzyme Linked Immunosorbent Assay).

35. The method according to any one of the preceding claims, wherein step (b) comprises or consists of measuring the presence and/or amount in the test sample of one or more of the biomarkers listed in Figure 1(E), Figure 2(D), Figure 2(H), Figure 3(D), Figure 3(E), Figure 3(F), Figure 4(A), Figure 5(A), Figure 5(B), Figure 8(A), Figure 8(B), Figure 8(C) and/or Figure 8(D).

36. An array for determining a systemic lupus erythematosus-associated disease state in an individual comprising one or more binding agent as defined in any one of Claims 24-29.

37. An array according to Claim 36 wherein the array is for use in a method according to any one of Claims 1-35.

38. An array according to Claim 36 or 37 wherein the array is as defined in any one of Claims 30-33.

39. An array according to any one of Claims 36-38 wherein the one or more binding agent is capable of binding to all of the proteins defined in Table A.

40. Use of one or more biomarkers selected from the group defined in Table A as a biomarker for determining a systemic lupus erythematosus-associated disease state in an individual.

41. The use according to Claim 40 wherein all of the biomarkers defined in Table A are used as a biomarker for determining a systemic lupus erythematosus-associated disease state in an individual.

42. Use of one or more binding agent as defined in any one of Claims 24-29 for determining a systemic lupus erythematosus-associated disease state in an individual.

43. The use according to Claim 42 wherein binding agents for all of the biomarkers defined in Table A are used for determining a systemic lupus erythematosus-associated disease state in an individual.

44. A kit for determining a systemic lupus erythematosus-associated disease state in an individual comprising:

i) one or more binding agent as defined in any one of Claims 24-29 or an array according to Claim 36-39,
ii) instructions for performing the method as defined in any one of Claims 1-35.

45. A method or use substantially as described herein.

46. An array or kit substantially as described herein.