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(54) Title: MONOCYTE BIOMARKERS FOR HYPERTENSION

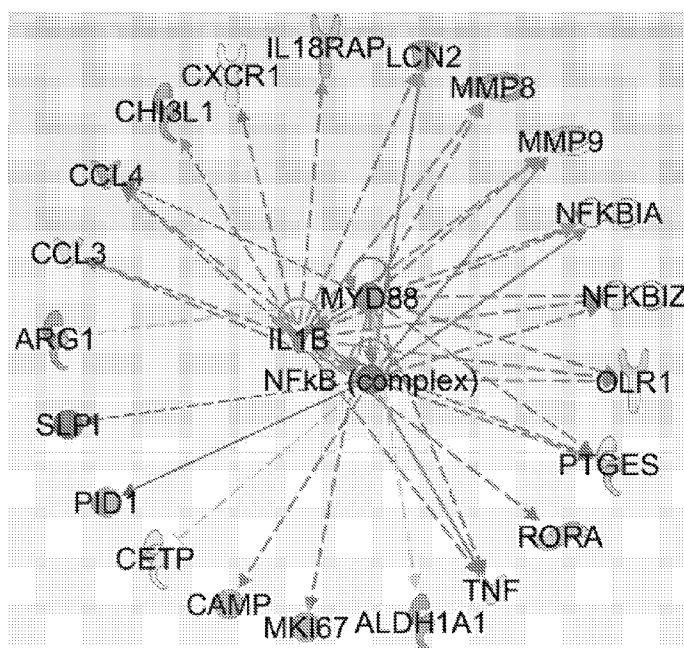


FIG. 1C

(57) Abstract: Provided herein are biomarkers for hypertension and inflammation in a subject being treated for hypertension and compositions and methods including the same.



**MONOCYTE BIOMARKERS FOR HYPERTENSION****CROSS-REFERENCE TO RELATED APPLICATIONS**

**[0001]** This application claims priority to U.S. Provisional Patent Application No. 62/489,821, filed April 25, 2017, which is incorporated herein by reference in its entirety.

**STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH**

**[0002]** This invention was made with government support under grant NHLBI K08 HL121671, T32 HL069765-11A1, and NHLBI K01 HL121045 awarded by the National Institutes of Health. The government has certain rights in the invention.

**FIELD**

**[0003]** This disclosure relates to biomarkers for hypertension and inflammation in hypertensive subjects and compositions and methods including the same.

**INTRODUCTION**

**[0004]** Despite conventional treatment, hypertension remains uncontrolled in nearly 50% of patients with the disease. Even when blood pressure is relatively controlled with conventional treatment, individuals with hypertension have an elevated risk of cardiovascular events such as myocardial infarction, stroke, heart failure, and chronic kidney disease. Therefore, there is a component of hypertension that is still insufficiently treated with conventional treatment.

**SUMMARY**

**[0005]** Provided herein are methods of diagnosing inflammation in a subject being treated for hypertension. The method may include (a) obtaining a sample from the subject; (b) determining a level of a biomarker in the sample; (c) comparing the level of the biomarker to a reference level of the biomarker; and (d) identifying the subject as having inflammation when the level of the biomarker is different from the reference level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

**[0006]** In some embodiments, the method further includes determining the level of at least one additional biomarker in the sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4. In some embodiments, the method further includes comparing the level of the at least one

additional biomarker to a reference level of the at least one additional biomarker; and identifying the subject as having inflammation when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker. In some embodiments, the subject is identified as having inflammation when (a) the level of IL18RAP in the sample is greater than the reference level of IL18RAP; (b) the level of LTF in the sample is greater than the reference level of LTF; (c) the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1; (d) the level of GZMH in the sample is greater than the reference level of GZMH; (e) the level of ARG1 in the sample is greater than the reference level of ARG1; (f) the level of MMP8 in the sample is greater than the reference level of MMP8; or (g) the level of VSIG4 in the sample is less than the reference level of VSIG4, or any combination of (a)-(g).

**[0007]** Provided herein are methods of determining if a subject being treated for hypertension has or is at risk of developing inflammation. The method may include (a) obtaining a sample from the subject; (b) determining a level of a biomarker in the sample; (c) comparing the level of the biomarker to a reference level of the biomarker; and (d) determining the subject has or is at risk of developing inflammation when the level of the biomarker is different from the reference level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

**[0008]** In some embodiments, the method further includes determining the level of at least one additional biomarker in the sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4.

**[0009]** In some embodiments, the method further includes comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker; and identifying the subject as having inflammation when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker. In some embodiments, the subject is determined to have or is at risk of developing inflammation when (a) the level of IL18RAP in the sample is greater than the reference level of IL18RAP; (b) the level of LTF in the sample is greater than the reference level of LTF; (c) the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1; (d) the level of GZMH in the sample is greater than the reference level of GZMH; (e) the level of ARG1 in the sample is greater than the reference level of ARG1; (f) the level of MMP8 in the sample is greater than the reference level of MMP8; or (g) the level of VSIG4 in the sample is less than the reference level of VSIG4, or any combination of (a)-(g).

**[0010]** Provided herein are methods of monitoring progression of inflammation in a subject being treated for hypertension. The method may include (a) obtaining first and second samples from the subject; (b) determining a first level of a biomarker in the first sample and a second level of the biomarker in the second sample; (c) comparing the first and second levels of the biomarker; and (d) determining: (i) inflammation has progressed in the subject when the second level of the biomarker is greater than the first level of the biomarker, or inflammation has not progressed in the subject when the second level of the biomarker is equivalent to or less than the first level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof; or (ii) inflammation has progressed in the subject when the second level of the biomarker is less than the first level of the biomarker, or inflammation has not progressed in the subject when the second level of the biomarker is equivalent to or greater than the first level of the biomarker, wherein the biomarker is VSIG4.

**[0011]** In some embodiments, the method further includes determining a first level of at least one additional biomarker in the first sample and a second level of the at least one additional biomarker in the second sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4. In some embodiments, the method further includes comparing the first and second levels of the at least one additional biomarker; and determining: (i) inflammation has progressed in the subject when the second level of the additional biomarker is greater than the first level of the additional biomarker, or inflammation has not progressed in the subject when the second level of the additional biomarker is equivalent to or less than the first level of the additional biomarker, wherein the additional biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8; or (ii) inflammation has progressed in the subject when the second level of the additional biomarker is less than the first level of the additional biomarker, or inflammation has not progressed in the subject when the second level of the additional biomarker is equivalent to or greater than the first level of the additional biomarker, wherein the additional biomarker is VSIG4.

**[0012]** Provided herein are methods of determining if a subject being treated for hypertension would benefit from anti-inflammatory therapy. The method may include (a) obtaining a sample from the subject; (b) determining a level of a biomarker in the sample; (c) comparing the level of the biomarker to a reference level of the biomarker; and (d) determining that the subject would benefit from anti-inflammatory therapy when the level of the biomarker is different from the reference level of the biomarker, wherein the biomarker is

selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

**[0013]** In some embodiments, the method further includes determining the level of at least one additional biomarker in the sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4. In some embodiments, the method further includes comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker; and determining that the subject would benefit from anti-inflammatory therapy when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker. In some embodiments, the subject is determined to likely benefit from anti-inflammatory therapy when: (a) the level of IL18RAP in the sample is greater than the reference level of IL18RAP; (b) the level of LTF in the sample is greater than the reference level of LTF; (c) the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1; (d) the level of GZMH in the sample is greater than the reference level of GZMH; (e) the level of ARG1 in the sample is greater than the reference level of ARG1; (f) the level of MMP8 in the sample is greater than the reference level of MMP8; or (g) the level of VSIG4 in the sample is less than the reference level of VSIG4, or any combination of (a)-(g).

**[0014]** Provided herein are methods of monitoring a subject's response to anti-inflammatory therapy, wherein the subject is being co-treated for hypertension. The method may include (a) obtaining first and second samples from the subject; (b) determining a first level of a biomarker in the first sample and a second level of the biomarker in the second sample; (c) comparing the first and second levels of the biomarker; and (d) determining: (i) the subject is not responding to the anti-inflammatory therapy when the second level of the biomarker is greater than the first level of the biomarker, or subject is responding to the anti-inflammatory therapy when the second level of the biomarker is equivalent to or less than the first level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof; or (ii) the subject is not responding to the anti-inflammatory therapy when the second level of the biomarker is less than the first level of the biomarker, or the subject is responding to the anti-inflammatory therapy when the second level of the biomarker is equivalent to or greater than the first level of the biomarker, wherein the biomarker is VSIG4.

**[0015]** In some embodiments, the method further includes determining a first level of at least one additional biomarker in the first sample and a second level of the at least one additional biomarker in the second sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4. In

some embodiments, the method further includes comparing the first and second levels of the at least one additional biomarker; and determining: (i) the subject is not responding to the anti-inflammatory therapy when the second level of the additional biomarker is greater than the first level of the additional biomarker, or the subject is responding to the anti-inflammatory therapy when the second level of the additional biomarker is equivalent to or less than the first level of the additional biomarker, wherein the additional biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8; or (ii) the subject is not responding to the anti-inflammatory therapy when the second level of the additional biomarker is less than the first level of the additional biomarker, or the subject is responding to the anti-inflammatory therapy when the second level of the additional biomarker is equivalent to or greater than the first level of the additional biomarker, wherein the additional biomarker is VSIG4.

**[0016]** Provided herein are methods of diagnosing hypertension in a subject. The method may include (a) obtaining a sample from the subject; (b) determining a level of a biomarker in the sample; (c) comparing the level of the biomarker to a reference level of the biomarker; and (d) identifying the subject as having hypertension when the level of the biomarker is different from the reference level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

**[0017]** In some embodiments, the method further includes determining the level of at least one additional biomarker in the sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4. In some embodiments, the method further includes comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker; and identifying the subject as having hypertension when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker. In some embodiments, the subject is identified as having hypertension when: (a) the level of IL18RAP in the sample is greater than the reference level of IL18RAP; (b) the level of LTF in the sample is greater than the reference level of LTF; (c) the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1; (d) the level of GZMH in the sample is greater than the reference level of GZMH; (e) the level of ARG1 in the sample is greater than the reference level of ARG1; (f) the level of MMP8 in the sample is greater than the reference level of MMP8; or (g) the level of VSIG4 in the sample is less than the reference level of VSIG4, or any combination of (a)-(g).

**[0018]** In some embodiments, the level of the biomarker in the sample is greater than the reference level of the biomarker, and wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof. In some embodiments, the level of the biomarker in the sample is less than the reference level of the biomarker, and wherein the biomarker is VSIG4. In some embodiments, the sample is a biological sample. In some embodiments, the sample is selected from whole blood, serum, and plasma. In some embodiments, the sample comprises monocytes. In some embodiments, determining the level of the biomarker in the sample includes detecting the biomarker with a technique selected from immunoassay, sequencing, and hybridization, or a combination thereof. In some embodiments, the reference level of the biomarker is the level of the biomarker in a control sample. In some embodiments, the reference level of the biomarker is a cutoff level. In some embodiments, the cutoff value is determined by a receiver operating curve (ROC) analysis from biological samples of a patient group. In some embodiments, the cutoff level is determined by a mean plus 2 standard deviation analysis of multiple control samples. In some embodiments, the subject is hypertensive. In some embodiments, the method further includes administering an anti-inflammation therapy to the subject. In some embodiments, the method further includes administering an anti-hypertension therapy to the subject.

**[0019]** Further provided are methods of treating inflammation in a subject being treated for hypertension. The method may include inhibiting the transcription, expression, or activity of, or a combination thereof, a gene or gene product selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof, or increasing the transcription, expression, or activity of, or a combination thereof, a gene or gene product selected from VSIG4.

**[0020]** Further provided are methods of treating hypertension in a subject. The method may include inhibiting the transcription, expression, or activity of, or a combination thereof, a gene or gene product selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof, or increasing the transcription, expression, or activity of, or a combination thereof, a gene or gene product selected from VSIG4.

**[0021]** Further provided are kits for detecting inflammation in a subject being treated for hypertension. The kit may include one or more reagents for detecting a biomarker selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

**[0022]** Further provided are kits for detecting hypertension in a subject. The kit may include one or more reagents for detecting a biomarker selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

**[0023]** Further provided are compositions including a probe array for detecting a biomarker in a sample. The array may include a plurality of probes that hybridizes to one or more biomarkers selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof. In some embodiments, the composition further includes a solid support with the plurality of probes attached thereto.

**[0024]** The disclosure provides for other aspects and embodiments that will be apparent in light of the following detailed description and accompanying figures.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**[0025]** **FIG. 1A, FIG. 1B, and FIG. 1C:** (**FIG. 1A**) Hierarchical clustering of normalized RPKM (reads per kilobase per million mapped reads) for those genes that were identified as significantly differentially expressed using RNASeq. Intensity of red or green is used to show fold increase or decrease, respectively. Columns represent individual samples, and each row represents one gene. (**FIG. 1B**) Principal components analysis (PCA) of the 60 significant genes. Three components were sufficient to describe 80.6% of the variability among samples (48.8%, 20.2%, and 11.6% on the X, Y, and Z axes, respectively). (**FIG. 1C**) Functional network generated from upstream regulator analysis using Ingenuity Pathway Analysis (IPA) software. The three central proteins were predicted to be activated using IPA (p values =  $1.5 \times 10^{-11}$  to  $1.5 \times 10^{-9}$ , Z scores = 2.9 to 3.9). Peripheral genes are overlaid with RNASeq expression values. Red or green color represents up- or down-regulation, respectively. Intensity of the color represents the degree of change. Orange lines with arrows indicate that directionality of the downstream gene is consistent with predicted activation of the up-stream regulator. Yellow lines indicate inconsistent results between gene expression and IPA's knowledge base for that particular interaction. Gray lines indicate that directionality cannot be resolved. Gene abbreviations are defined in **TABLE 3**.

**[0026]** **FIG. 2A, FIG. 2B, FIG. 2C, and FIG. 2D:** Univariate regressions of mean arterial pressure (MAP) and the expression ( $\log_{10}$ RPKM) of those genes that significantly correlated with MAP in multivariate regression analyses: (**FIG. 2A**) lactoferrin (LTF) (**FIG. 2B**) peptidoglycan recognition protein 1 (PGLYRP1), (**FIG. 2C**) granzyme H (GZMH) and (**FIG. 2D**) interleukin 18 receptor accessory protein (IL18RAP). Control normotensive subjects are represented by open dots, and hypertensive patients are shown by closed dots.

Pearson correlation coefficients and their significance are given for controls (C, n=5), hypertensive subjects (HTN, n=7) or all subjects analyzed together (All, n=12).  $P < 0.05$  was considered significant.

**[0027]** FIG. 3A, FIG. 3B, FIG. 3C, and FIG. 3D: Relative RT-PCR quantification (normalized to GAPDH) of (FIG. 3A) lactoferrin (LTF) (FIG. 3B) peptidoglycan recognition protein 1 (PGLYRP1) (FIG. 3C) granzyme H (GZMH), and (FIG. 3D) interleukin 18 receptor accessory protein (IL18RAP) in a validation cohort of normotensive (n=6) and hypertensive (n=9) patients. Data are plotted as mean $\pm$ SEM. \* $P < 0.05$  by Student's t-test or Mann-Whitney test.

**[0028]** FIG. 4A and FIG. 4B: Correlation between mean arterial pressure (MAP) and IL18RAP expression (FIG. 4A) and between eGFR and IL18RAP expression (FIG. 4B) in hypertensive individuals (n=76). Pearson correlation coefficients and statistical significance are given in the graphs.

**[0029]** FIG. 5: PheWAS Manhattan plot for the LTF SNP rs1126478 showing association between this SNP and 1,416 different phenotypes. Disease groups on the x-axis are shown in different colors, and the y-axis reflects the p value for each phenotype. Purple and orange horizontal lines represent p value of 0.05 and Bonferroni corrected p value of  $3.5 \times 10^{-5}$ , respectively.

**[0030]** FIG. 6A, FIG. 6B, FIG. 6C, and FIG. 6D: Relative RT-PCR quantification (normalized to GAPDH) of (FIG. 6A) arginase 1 (Arg1), (FIG. 6B) chemokine (C-C motif) ligand 4 (CCL4), (FIG. 6C) matrix metalloproteinase 8 (MMP8), and (FIG. 6D) V-set and immunoglobulin domain containing 4 (VSIG4) in a validation cohort of control normotensive (n=6) and hypertensive (n=9) patients. Data are plotted as mean $\pm$ SEM. \* $P < 0.05$  by one-tailed Mann-Whitney test.

**[0031]** FIG. 7. Graphs showing that IL18RAP is positively and negatively correlated with MAP and eGFR (n =76), respectively.

**[0032]** FIG. 8. Graphs showing that eGFR is negatively correlated with PGLYRP1 expression.

**[0033]** FIG. 9. A PheWAS (phenome-wide association studies) Manhattan plot for SNP rs1126478 in LTF. This plot shows association between SNP rs1126478 and 1345 different phenotypes. Along the X-axis different disease groups are shown in different colors. The Y-

axis reflects the P value for each phenotype. Blue and red horizontal lines represent P value of 0.05 and Bonferroni corrected P value of  $5.8 \times 10^{-5}$ , respectively.

## DETAILED DESCRIPTION

**[0034]** The present disclosure relates to biomarkers for hypertension and for inflammation in subjects being treated for hypertension. Treated hypertension is associated with a pro-inflammatory gene signature in monocytes. These transcripts may serve as biomarkers for disease severity or as potential novel therapeutic targets. Provided herein are methods for detecting and/or quantifying the levels of biomarkers including, for example, IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, or VSIG4, or a combination thereof. The level of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, or MMP8 may be greater in a subject suffering from, or at risk of suffering from, hypertension or inflammation as compared to a subject not suffering from, or at risk of suffering from, hypertension or inflammation. The level of VSIG4 may be less in a subject suffering from, or at risk of suffering from, hypertension or inflammation as compared to a subject not suffering from, or at risk of suffering from, hypertension or inflammation. The subject suffering from inflammation may also be undergoing treatment for hypertension. The methods disclosed herein may be used for identifying, diagnosing, detecting, prognosing, classifying risk, treating, and/or monitoring the progression of hypertension and/or inflammation.

### 1. Definitions

**[0035]** The terms "comprise(s)," "include(s)," "having," "has," "can," "contain(s)," and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that do not preclude the possibility of additional acts or structures. The singular forms "a," "and," and "the" include plural references unless the context clearly dictates otherwise. The present disclosure also contemplates other embodiments "comprising," "consisting of," and "consisting essentially of," the embodiments or elements presented herein, whether explicitly set forth or not.

**[0036]** For the recitation of numeric ranges herein, each intervening number there between with the same degree of precision is explicitly contemplated. For example, for the range of 6-9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the number 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, and 7.0 are explicitly contemplated.

**[0037]** Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. In case of

conflict, the present document, including definitions, will control. Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can be used in practice or testing of the present invention. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting.

**[0038]** The term “about” as used herein as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain aspects, the term “about” refers to a range of values that fall within 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

**[0039]** The term “administration” or “administering,” as used herein, refers to providing, contacting, and/or delivery of an agent by any appropriate route to achieve the desired effect. These agents may be administered to a subject in numerous ways including, but not limited to, orally, ocularly, nasally, intravenously, topically, as aerosols, suppository, etc. and may be used in combination.

**[0040]** The term “agonist” refers to a biologically active ligand that binds to its complementary biologically active receptor and activates the receptor either to cause a biological response in the receptor or to enhance a biological activity of the receptor. An agonist may trigger (e.g., initiate or promote), partially or fully enhance, stimulate, increase, or activate one or more biological activities. An agonist may mimic the action of a naturally occurring substance.

**[0041]** “Antagonist” or “inhibitor” may be used interchangeably herein and refers to an agent that inhibits the effect of an agonist. An antagonist may be a compound that inhibits or reduces an activity of a polypeptide. An antagonist may indirectly or directly bind a polypeptide and inhibit the activity of the polypeptide, including binding activity or catalytic activity. For example, an antagonist may prevent transcription of a gene encoding a polypeptide, an antagonist may prevent expression of a polypeptide, or an antagonist may inhibit the ability of a polypeptide to catalyze a reaction or mediate the binding of the polypeptide to a ligand. An “allosteric antagonist” refers to a compound that binds to a polypeptide at a secondary site, distinct from the primary ligand binding site, and inhibits or reduces an activity of the polypeptide. The terms “inhibit” or “inhibiting” mean that an activity

is decreased or prevented in the presence of an inhibitor as opposed to in the absence of the inhibitor. The term "inhibition" refers to the reduction or down regulation of a process or the elimination of a stimulus for a process, which results in the absence or minimization of the expression or activity of a biomolecule or polypeptide. Inhibition may be direct or indirect. Inhibition may be specific, that is, the inhibitor inhibits a biomolecule or polypeptide and not others.

**[0042]** "Amino acid" as used herein refers to naturally occurring and non-natural synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code. Amino acids can be referred to herein by either their commonly known three-letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Amino acids include the side chain and polypeptide backbone portions.

**[0043]** The "area under curve" or "AUC" refers to area under a ROC curve. AUC under a ROC curve is a measure of accuracy. An area of 1 represents a perfect test, whereas an area of 0.5 represents an insignificant test. A preferred AUC may be at least approximately 0.700, at least approximately 0.750, at least approximately 0.800, at least approximately 0.850, at least approximately 0.900, at least approximately 0.910, at least approximately 0.920, at least approximately 0.930, at least approximately 0.940, at least approximately 0.950, at least approximately 0.960, at least approximately 0.970, at least approximately 0.980, at least approximately 0.990, or at least approximately 0.995.

**[0044]** "Component," "components," or "at least one component," refer generally to a capture antibody, a detection conjugate, a calibrator, a control, a sensitivity panel, a container, a buffer, a diluent, a salt, an enzyme, a co-factor for an enzyme, a detection reagent, a pretreatment reagent/solution, a substrate (e.g., as a solution), a stop solution, and the like that can be included in a kit for assay of a test sample, in accordance with the methods described herein and other methods known in the art. Some components can be in solution or lyophilized for reconstitution for use in an assay.

**[0045]** The terms "control," "reference level," and "reference" may be used herein interchangeably. The reference level may be a predetermined value or range, which is employed as a benchmark against which to assess the measured result. "Control group" as used herein refers to a group of control subjects. The predetermined level may be a cutoff value from a control group. The predetermined level may be an average from a control group. Cutoff values (or predetermined cutoff values) may be determined by Adaptive Index

Model (AIM) methodology. Cutoff values (or predetermined cutoff values) may be determined by a receiver operating curve (ROC) analysis from biological samples of the patient group. ROC analysis, as generally known in the biological arts, is a determination of the ability of a test to discriminate one condition from another, e.g., to determine the performance of each marker in identifying a patient having CRC. A description of ROC analysis is provided in P.J. Heagerty et al. (*Biometrics* **2000**, 56, 337-44), the disclosure of which is hereby incorporated by reference in its entirety. Alternatively, cutoff values may be determined by a quartile analysis of biological samples of a patient group. For example, a cutoff value may be determined by selecting a value that corresponds to any value in the 25th-75th percentile range, preferably a value that corresponds to the 25th percentile, the 50th percentile or the 75th percentile, and more preferably the 75th percentile. Such statistical analyses may be performed using any method known in the art and can be implemented through any number of commercially available software packages (e.g., from Analyse-it Software Ltd., Leeds, UK; StataCorp LP, College Station, TX; SAS Institute Inc., Cary, NC.). The healthy or normal levels or ranges for a target or for a protein activity may be defined in accordance with standard practice. A control may be a subject, or a sample therefrom, whose disease state is known. The subject, or sample therefrom, may be healthy, diseased, diseased prior to treatment, diseased during treatment, or diseased after treatment, or a combination thereof. The term "normal subject" as used herein means a healthy subject, i.e. a subject having no clinical signs or symptoms of disease. The normal subject may be clinically evaluated for otherwise undetected signs or symptoms of disease, which evaluation may include routine physical examination and/or laboratory testing. In some embodiments, the control is a healthy control. In some embodiments, the control is from a subject having hypertension. In some embodiments, the control is from a subject having inflammation.

**[0046]** The term "expression vector" indicates a plasmid, a virus or another medium, known in the art, into which a nucleic acid sequence for encoding a desired protein can be inserted or introduced.

**[0047]** The term "host cell" is a cell that is susceptible to transformation, transfection, transduction, conjugation, and the like with a nucleic acid construct or expression vector. Host cells can be derived from plants, bacteria, yeast, fungi, insects, animals, etc.

**[0048]** "Label" and "detectable label" as used herein refer to a moiety attached to an antibody or an analyte to render the reaction between the antibody and the analyte detectable, and the antibody or analyte so labeled is referred to as "detectably labeled." A label can produce a signal that is detectable by visual or instrumental means. Various labels

include signal-producing substances, such as chromagens, fluorescent compounds, chemiluminescent compounds, radioactive compounds, and the like. Representative examples of labels include moieties that produce light, e.g., acridinium compounds, and moieties that produce fluorescence, e.g., fluorescein. Other labels are described herein. In this regard, the moiety, itself, may not be detectable but may become detectable upon reaction with yet another moiety. Use of the term "detectably labeled" is intended to encompass such labeling.

**[0049]** Any suitable detectable label as is known in the art can be used. For example, the detectable label can be a radioactive label (such as  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{32}\text{P}$ ,  $^{33}\text{P}$ ,  $^{35}\text{S}$ ,  $^{90}\text{Y}$ ,  $^{99}\text{Tc}$ ,  $^{111}\text{In}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{177}\text{Lu}$ ,  $^{166}\text{Ho}$ , and  $^{153}\text{Sm}$ ), an enzymatic label (such as horseradish peroxidase, alkaline peroxidase, glucose 6-phosphate dehydrogenase, and the like), a chemiluminescent label (such as acridinium esters, thioesters, or sulfonamides; luminol, isoluminol, phenanthridinium esters, and the like), a fluorescent label (such as fluorescein (e.g., 5-fluorescein, 6-carboxyfluorescein, 3'-carboxyfluorescein, 5(6)-carboxyfluorescein, 6-hexachloro-fluorescein, 6-tetrachlorofluorescein, fluorescein isothiocyanate, and the like)), rhodamine, phycobiliproteins, R-phycoerythrin, quantum dots (e.g., zinc sulfide-capped cadmium selenide), a thermometric label, or an immuno-polymerase chain reaction label. Examples of preferred fluorophores include, but are not limited to, 7-amino-4-methylcoumarin-3-acetic acid (AMCA), 5-carboxy-X-rhodamine, 6-carboxy-X-rhodamine, lissamine rhodamine B, 5-carboxyfluorescein, 6-carboxyfluorescein, fluorescein-5-isothiocyanate (FITC), 7-diethylaminocoumarin-3-carboxylic acid, tetramethylrhodamine-5-isothiocyanate, tetramethylrhodamine-6-isothiocyanate, 5-carboxyltetramethylrhodamine, 6-carboxytetramethylrhodamine, 7-hydroxycoumarin-3-carboxylic acid, N-4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-3-indacenepropionic acid, eosin-5-isothiocyanate, erythrosine-5-isothiocyanate, TEXAS RED (Molecular Probes, Inc.), and CASCADE blue acetylazide (Molecular Probes, Inc.). An introduction to labels, labeling procedures and detection of labels is found in Polak and Van Noorden, *Introduction to Immunocytochemistry*, 2nd ed., Springer Verlag, N.Y. (1997), and in Haugland, *Handbook of Fluorescent Probes and Research Chemicals* (1996), which is a combined handbook and catalogue published by Molecular Probes, Inc., Eugene, Oregon. A fluorescent label can be used in FPIA (see, e.g., U.S. Patent Nos. 5,593,896, 5,573,904, 5,496,925, 5,359,093, and 5,352,803, which are hereby incorporated by reference in their entireties). An acridinium compound can be used as a detectable label in a homogeneous chemiluminescent assay (see, e.g., Adamczyk et al., *Bioorg. Med. Chem. Lett.* 2006, 16, 1324-1328; Adamczyk et al., *Bioorg. Med. Chem. Lett.* 2004, 4, 2313-2317; Adamczyk et al., *Bioorg. Med. Chem. Lett.* 2004, 14, 3917-3921; and Adamczyk et al., *Org. Lett.* 2003, 5, 3779-3782).

**[0050]** In one aspect, the acridinium compound is an acridinium-9-carboxamide. Methods for preparing acridinium 9-carboxamides are described in Mattingly, J. *Biolumin. Chemilumin.* 1991, 6, 107-114; Adamczyk et al., *J. Org. Chem.* 1998, 63, 5636-5639; Adamczyk et al., *Tetrahedron* 1999, 55, 10899-10914; Adamczyk et al., *Org. Lett.* 1999, 1, 779-781; Adamczyk et al., *Bioconjugate Chem.* 2000, 11, 714-724; Mattingly et al., In *Luminescence Biotechnology: Instruments and Applications*; Dyke, K. V. Ed.; CRC Press: Boca Raton, pp. 77-105 (2002); Adamczyk et al., *Org. Lett.* 2003, 5, 3779-3782; and U.S. Pat. Nos. 5,468,646, 5,543,524 and 5,783,699 (each of which is incorporated herein by reference in its entirety for its teachings regarding same).

**[0051]** Another example of an acridinium compound is an acridinium-9-carboxylate aryl ester. An example of an acridinium-9-carboxylate aryl ester is 10-methyl-9-(phenoxycarbonyl)acridinium fluorosulfonate (available from Cayman Chemical, Ann Arbor, MI). Methods for preparing acridinium 9-carboxylate aryl esters are described in McCapra et al., *Photochem. Photobiol.* 1965, 4, 1111-21; Razavi et al., *Luminescence* 2000, 15, 245-249; Razavi et al., *Luminescence* 2000, 15, 239-244; and U.S. Patent No. 5,241,070 (each of which is incorporated herein by reference in its entirety for its teachings regarding same). Such acridinium-9-carboxylate aryl esters are efficient chemiluminescent indicators for hydrogen peroxide produced in the oxidation of an analyte by at least one oxidase in terms of the intensity of the signal and/or the rapidity of the signal. The course of the chemiluminescent emission for the acridinium-9-carboxylate aryl ester is completed rapidly, i.e., in under 1 second, while the acridinium-9-carboxamide chemiluminescent emission extends over 2 seconds. Acridinium-9-carboxylate aryl ester, however, loses its chemiluminescent properties in the presence of protein. Therefore, its use requires the absence of protein during signal generation and detection. Methods for separating or removing proteins in the sample are well-known to those skilled in the art and include, but are not limited to, ultrafiltration, extraction, precipitation, dialysis, chromatography, and/or digestion (see, e.g., Wells, *High Throughput Bioanalytical Sample Preparation. Methods and Automation Strategies*, Elsevier 2003). The amount of protein removed or separated from the test sample can be about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%. Acridinium-9-carboxylate aryl esters can be dissolved in any suitable solvent, such as degassed anhydrous N,N-dimethylformamide (DMF) or aqueous sodium cholate.

**[0052]** "Polynucleotide" as used herein can be single stranded or double stranded, or can contain portions of both double stranded and single stranded sequence. The polynucleotide can be nucleic acid, natural or synthetic, DNA, genomic DNA, cDNA, RNA, or

a hybrid, where the polynucleotide can contain combinations of deoxyribo- and ribonucleotides, and combinations of bases including uracil, adenine, thymine, cytosine, guanine, inosine, xanthine hypoxanthine, isocytosine, and isoguanine. Polynucleotides may include siRNA. Polynucleotides include the complements thereof. Polynucleotides can be obtained by chemical synthesis methods or by recombinant methods.

**[0053]** As used herein, the term “gene” means the polynucleotide sequence comprising the coding region of a gene, e.g., a structural gene, and the including sequences located adjacent to the coding region on both the 5' and 3' ends for a distance of about 1 kb on either end such that the gene corresponds to the length of the full-length mRNA. The sequences which are located 5' or upstream of the coding region and which are present on the mRNA are referred to as 5' non-translated sequences. The sequences which are located 3' or downstream of the coding region and which are present on the mRNA are referred to as 3' non-translated sequences. The term “gene” encompasses both cDNA and genomic forms of a gene. A genomic form or clone of a gene contains the coding region interrupted with non-coding sequences termed “introns” or “intervening regions” or “intervening sequences.” Introns are segments of a gene which are transcribed into nuclear RNA, for example, heterogeneous nuclear RNA (hnRNA); introns may contain regulatory elements such as enhancers. Introns are removed or “spliced out” from the nuclear or primary transcript; introns therefore are absent in the messenger RNA (mRNA) transcript. The mRNA functions during translation to specify the sequence or order of amino acids in a nascent polypeptide. In addition to containing introns, genomic forms of a gene may also include sequences located on both the 5' and 3' end of the sequences which are present on the RNA transcript. These sequences are referred to as “flanking” sequences or regions (these flanking sequences are located 5' or 3' to the non-translated sequences present on the mRNA transcript). The 5' flanking region may contain regulatory sequences such as promoters and enhancers which control or influence the transcription of the gene. The 3' flanking region may contain sequences which direct the termination of transcription, post-transcriptional cleavage and polyadenylation.

**[0054]** As used herein, an oligonucleotide or polynucleotide “having a nucleotide sequence encoding a gene” means a polynucleotide sequence comprising the coding region of a gene, or in other words, the nucleic acid sequence which encodes a gene product. The coding region may be present in either a cDNA, genomic DNA, or RNA form. When present in a DNA form, the oligonucleotide may be single-stranded (i.e., the sense strand) or double-stranded. Suitable control elements such as enhancers/promoters, splice junctions, polyadenylation signals, etc. may be placed in close proximity to the coding region of the

gene if needed to permit proper initiation of transcription and/or correct processing of the primary RNA transcript. Alternatively, the coding region utilized in the vector may contain endogenous enhancers/promoters, splice junctions, intervening sequences, polyadenylation signals, etc., or a combination of both endogenous and exogenous control elements.

**[0055]** A "peptide" or "polypeptide" is a linked sequence of amino acids and can be natural, synthetic, or a modification or combination of natural and synthetic. Peptides and polypeptides include proteins such as binding proteins, receptors, and antibodies. "Primary structure" refers to the amino acid sequence of a particular peptide. "Secondary structure" refers to locally ordered, three dimensional structures within a polypeptide. These structures are commonly known as domains, e.g., enzymatic domains, extracellular domains, transmembrane domains, pore domains, and cytoplasmic tail domains. Domains are portions of a polypeptide that form a compact unit of the polypeptide and are typically 15 to 350 amino acids long. Exemplary domains include domains with enzymatic activity or ligand binding activity. Typical domains are made up of sections of lesser organization such as stretches of beta-sheet and alpha-helices. "Tertiary structure" refers to the complete three dimensional structure of a polypeptide monomer. "Quaternary structure" refers to the three dimensional structure formed by the noncovalent association of independent tertiary units.

**[0056]** "Predetermined cutoff" and "predetermined level" as used herein refer to an assay cutoff value that is used to assess diagnostic, prognostic, or therapeutic efficacy results by comparing the assay results against the predetermined cutoff/level, where the predetermined cutoff/level already has been linked or associated with various clinical parameters (e.g., presence of disease, stage of disease, severity of disease, progression, non-progression, or improvement of disease, etc.). Cutoff values may vary depending on the nature of the immunoassay (e.g., antibodies employed, reaction conditions, sample purity, etc.). It is well within the ordinary skill of one in the art to adapt the disclosure herein for other immunoassays to obtain immunoassay-specific cutoff values for those other immunoassays based on the description provided by this disclosure. Whereas the precise value of the predetermined cutoff/level may vary between assays, the correlations as described herein should be generally applicable.

**[0057]** "Probe," as used herein, is an oligonucleotide or polynucleotide that can selectively hybridize to at least a portion of a target sequence under conditions that allow for or promote selective hybridization. In general, a probe can be complementary to the coding or sense (+) strand of DNA or complementary to the non-coding or anti-sense (-) strand of DNA (sometimes referred to as "reverse complementary"). Probes can vary significantly in

length. For example, a probe may be a length of about 10 to about 100 nucleotides, about 15 to about 75 nucleotides, or about 15 to about 50 nucleotides.

**[0058]** “Recombinant” when used with reference, e.g., to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein, or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed, or not expressed at all.

**[0059]** “Risk assessment,” “risk classification,” “risk identification,” or “risk stratification” of subjects (e.g., patients) as used herein refers to the evaluation of factors including biomarkers, to predict the risk of occurrence of future events including disease onset or disease progression, so that treatment decisions regarding the subject may be made on a more informed basis.

**[0060]** “Sample” or “biological sample” or “test sample” as used herein can mean any sample in which the presence and/or level of a biomarker is to be detected or determined. Samples may include a medical sample. Samples may include any biological fluid or tissue, such as blood, whole blood, fractions of blood such as plasma and serum, muscle, interstitial fluid, sweat, saliva, urine, tears, synovial fluid, bone marrow, cerebrospinal fluid, nasal secretions, sputum, amniotic fluid, bronchoalveolar lavage fluid, lung tissue, peripheral blood mononuclear cells (PBMC), total white blood cells, monocytes, lymph node cells, spleen cells, tonsil cells, skin, or combinations thereof. In some embodiments, the sample comprises a biological fluid. In some embodiments, the sample comprises blood, whole blood, plasma, serum, PBMCs, monocytes, or a combination thereof. In some embodiments, the sample comprises blood, PBMCs, monocytes, or a combination thereof. In some embodiments, the sample comprises monocytes. Monocytes may be isolated from whole blood. Samples can be obtained by any means known in the art. The sample can be used directly as obtained from a patient or can be pre-treated, such as by filtration, distillation, extraction, concentration, centrifugation, inactivation of interfering components, addition of reagents, and the like, to modify the character of the sample in some manner as discussed herein or otherwise as is known in the art.

**[0061]** “Series of calibrating compositions” refers to a plurality of compositions comprising a known concentration or levels of biomarkers, wherein each of the compositions differs from the other compositions in the series by the concentration of the biomarker.

**[0062]** "Selectively hybridize to" (as well as "selective hybridization," "specifically hybridize to," and "specific hybridization"), as used herein, refers to the binding, duplexing, or hybridizing of a polynucleotide preferentially to a particular nucleotide sequence under stringent conditions. The term "stringent conditions" refers to conditions under which a probe will hybridize preferentially to its target sequence, and to a lesser extent to, or not at all to, other non-target sequences. A "stringent hybridization" and "stringent hybridization wash conditions" in the context of nucleic acid hybridization (e.g., as in array, Southern hybridization, Northern hybridization, or FISH) are sequence-dependent, and differ under different conditions. An extensive guide to the hybridization of nucleic acids is found in, e.g., Tijssen, 25 Laboratory Techniques in Biochemistry and Molecular Biology--Hybridization with Nucleic Acid Probes, Part I, Ch. 2, "Overview of principles of hybridization and the strategy of nucleic acid probe assays," Elsevier, NY (1993) ("Tijssen "). Generally, highly stringent hybridization and wash conditions are selected to be about 5°C lower than the thermal melting point ( $T_m$ ) for the specific sequence at a defined ionic strength and pH. The  $T_m$  is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. Very stringent conditions are selected to be equal to the  $T_m$  for a particular probe. An example of stringent hybridization conditions for hybridization of complementary polynucleotides, which have more than 100 complementary residues, on an array or on a filter in a Southern or Northern blot is 42°C using standard hybridization solutions (see, e.g., Sambrook and Russell, Molecular Cloning: A Laboratory Manual, 3rd ed., Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, NY (2001)).

**[0063]** The term "sensitivity" as used herein refers to the number of true positives divided by the number of true positives plus the number of false negatives, where sensitivity ("sens") may be within the range of  $0 < \text{sens} < 1$ . Ideally, method embodiments herein have the number of false negatives equaling zero or close to equaling zero, so that no subject is wrongly identified as not having hypertension or inflammation when they indeed have hypertension or inflammation. Conversely, an assessment often is made of the ability of a prediction algorithm to classify negatives correctly, a complementary measurement to sensitivity.

**[0064]** The term "specificity" as used herein refers to the number of true negatives divided by the number of true negatives plus the number of false positives, where specificity ("spec") may be within the range of  $0 < \text{spec} < 1$ . Ideally, the methods described herein have the number of false positives equaling zero or close to equaling zero, so that no subject is wrongly identified as having hypertension or inflammation when they do not in fact have

hypertension or inflammation. Hence, a method that has both sensitivity and specificity equaling one, or 100%, is preferred.

**[0065]** By “specifically binds,” it is generally meant that a polypeptide or biosensor, or derivative thereof, binds to a ligand when it binds to that ligand via its ligand-binding site more readily than it would bind to a random, unrelated ligand.

**[0066]** “Subject” or “patient” as used herein refers to any subject, particularly a mammalian subject, who wants to or is in need of detecting a biomarker. The subject may be a human or a non-human animal. The subject may be a mammal. The mammal may be a primate or a non-primate. The mammal can be a primate such as a human; a non-primate such as, for example, dog, cat, horse, cow, pig, mouse, rat, camel, llama, goat, rabbit, sheep, hamster, and guinea pig; or non-human primate such as, for example, monkey, chimpanzee, gorilla, orangutan, and gibbon. The subject may be of any age or stage of development, such as, for example, an adult, an adolescent, or an infant. In some embodiments, the subject is human. In some embodiments, the subject has a specific genetic marker.

**[0067]** “Substantially identical” can mean that a first and second amino acid sequence are at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% over a region of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100 amino acids.

**[0068]** “Target” as used herein can refer to an entity that a drug molecule or therapy binds or affects. A target may include, for example, a small molecule, a protein, a polypeptide, a polynucleotide, a carbohydrate, or a combination thereof.

**[0069]** A “therapeutically effective amount,” or “effective dosage,” or “effective amount” as used interchangeably herein unless otherwise defined, means a dosage of an agent or drug effective for periods of time necessary, to achieve the desired therapeutic result. An effective dosage may be determined by a person skilled in the art and may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the drug to elicit a desired response in the individual. This term as used herein may also refer to an amount effective at bringing about a desired *in vivo* effect in a subject. A therapeutically effective amount may be administered in one or more administrations (e.g., the composition may be given as a preventative treatment or therapeutically at any stage of disease progression, before or after symptoms, and the like), applications, or dosages, and is not

intended to be limited to a particular formulation, combination, or administration route. It is within the scope of the present disclosure that the drug may be administered at various times during the course of treatment of the subject. The times of administration and dosages used will depend on several factors, such as the goal of treatment (e.g., treating v. preventing), condition of the subject, etc. and can be readily determined by one skilled in the art. A therapeutically effective amount is also one in which any toxic or detrimental effects of substance are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

**[0070]** The terms "treat," "treated," or "treating" as used herein refers to a therapeutic wherein the object is to slow down (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. The terms "treat," "treated," or "treating" may include preventing, suppressing, repressing, ameliorating, or completely eliminating the disease. Preventing the disease may involve administering a composition of the present invention to a subject prior to onset of the disease. Suppressing the disease may involve administering a composition of the present invention to a subject after induction of the disease but before its clinical appearance. Repressing or ameliorating the disease may involve administering a composition of the present invention to a subject after clinical appearance of the disease.

**[0071]** "Variant" used herein with respect to a polynucleotide means (i) a portion or fragment of a referenced nucleotide sequence; (ii) the complement of a referenced nucleotide sequence or portion thereof; (iii) a polynucleotide that is substantially identical to a referenced polynucleotide or the complement thereof; or (iv) a polynucleotide that hybridizes under stringent conditions to the referenced polynucleotide, complement thereof, or a sequences substantially identical thereto.

**[0072]** A “variant” can further be defined as a peptide or polypeptide that differs in amino acid sequence by the insertion, deletion, or conservative substitution of amino acids, but retain at least one biological activity. Representative examples of “biological activity” include the ability to be bound by a specific antibody or to promote an immune response. Variant can mean a substantially identical sequence. Variant can mean a functional fragment thereof. Variant can also mean multiple copies of a polypeptide. The multiple copies can be in tandem or separated by a linker. Variant can also mean a polypeptide with an amino acid sequence that is substantially identical to a referenced polypeptide with an amino acid sequence that retains at least one biological activity. A conservative substitution of an amino acid, i.e., replacing an amino acid with a different amino acid of similar properties (e.g., hydrophilicity, degree and distribution of charged regions) is recognized in the art as typically involving a minor change. These minor changes can be identified, in part, by considering the hydropathic index of amino acids. See Kyte et al., *J. Mol. Biol.* **1982**, 157, 105-132. The hydropathic index of an amino acid is based on a consideration of its hydrophobicity and charge. It is known in the art that amino acids of similar hydropathic indexes can be substituted and still retain protein function. In one aspect, amino acids having hydropathic indexes of  $\pm 2$  are substituted. The hydrophobicity of amino acids can also be used to reveal substitutions that would result in polypeptides retaining biological function. A consideration of the hydrophilicity of amino acids in the context of a polypeptide permits calculation of the greatest local average hydrophilicity of that polypeptide, a useful measure that has been reported to correlate well with antigenicity and immunogenicity, as discussed in U.S. Patent No. 4,554,101, which is fully incorporated herein by reference. Substitution of amino acids having similar hydrophilicity values can result in polypeptides retaining biological activity, for example immunogenicity, as is understood in the art. Substitutions can be performed with amino acids having hydrophilicity values within  $\pm 2$  of each other. Both the hydrophobicity index and the hydrophilicity value of amino acids are influenced by the particular side chain of that amino acid. Consistent with that observation, amino acid substitutions that are compatible with biological function are understood to depend on the relative similarity of the amino acids, and particularly the side chains of those amino acids, as revealed by the hydrophobicity, hydrophilicity, charge, size, and other properties.

**[0073]** A variant can be a polynucleotide sequence that is substantially identical over the full length of the full gene sequence or a fragment thereof. The polynucleotide sequence can be 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical over the full length of the gene sequence or a fragment thereof. A variant can be an amino acid sequence that is substantially identical over the full length of the amino acid sequence or fragment thereof.

The amino acid sequence can be 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical over the full length of the amino acid sequence or a fragment thereof.

## **2. Disease**

**[0074]** The present disclosure relates to analyzing or quantifying the levels of one or more biomarkers for diagnosing, prognosing, classifying risk, and monitoring the progression or severity of a disease. The biomarkers may be used as targets for treating or preventing a disease. The disease may include hypertension, inflammation in a subject being treated for hypertension, end organ damage from hypertension, or a combination thereof.

### **a. Hypertension**

**[0075]** Hypertension is also known as high blood pressure. Hypertension is a long term medical condition in which the blood pressure in the arteries is persistently elevated. Blood pressure may be expressed by two measurements, the systolic pressure and the diastolic pressure, which are the maximum and minimum pressures, respectively, in the arterial system. The systolic pressure occurs when the left ventricle is most contracted. The diastolic pressure occurs when the left ventricle is most relaxed prior to the next contraction. Normal blood pressure may be about 100 to about 130 millimeters mercury (mmHg) systolic and about 60 to about 80 mmHg diastolic. Hypertension may result when the resting blood pressure is persistently at or above 130/80 mmHg in a human adult.

**[0076]** Hypertension may be classified as primary (also referred to as essential) hypertension or secondary hypertension. Primary hypertension is high blood pressure with no obvious underlying cause. Secondary hypertension is hypertension due to an identifiable cause, such as, for example, renal failure, chronic kidney disease, narrowing of the aorta or kidney arteries, cancer, pregnancy, anemia, atherosclerosis, scleroderma, neurological disorder, obstructive sleep apnea, neurofibromatosis, Cushing's syndrome, acromegaly, hypothyroidism, hyperthyroidism, hyperparathyroidism, or an endocrine disorder such as excess aldosterone, cortisol, or catecholamines.

**[0077]** Sustained hypertension over time may be a risk factor for many cardiovascular events, disorders, or conditions, such as, for example, hypertensive heart disease, heart failure, coronary artery disease, myocardial infarction, stroke, aortic aneurysm, peripheral artery disease, and chronic kidney disease. Even when blood pressure is relatively controlled, hypertensive patients are still at an elevated risk of cardiovascular events.

**[0078]** Therapies may include hypertension therapy. Drugs used in therapies for hypertension include, for example, thiazide-diuretics, calcium channel blockers, spironolactone, angiotensin converting enzyme inhibitors, neprilysin inhibitors, angiotensin receptor blockers, and combination angiotensin receptor blockers/neprilysin inhibitors. Hypertension treatment may include dietary and lifestyle changes, which may lower blood pressure and decrease the risk of health complications.

#### **b. Inflammation**

**[0079]** Inflammation is a protective response that involves immune cells, blood vessels, and molecular mediators. Inflammation may refer to an enlargement of organs, tissues, and/or cells caused by an immune response to injury or antigens. The purpose of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair. In some embodiments, the subject having inflammation or at risk of developing inflammation is currently or was previously being treated for hypertension. Hypertension may be an inflammatory disease in which antigen presenting cells, particularly monocyte-derived dendritic cells, present neo-antigens to T lymphocytes, which then leads to T cell activation, infiltration of target organs, and the production of pro-inflammatory cytokines that cause sodium and water retention, vascular dysfunction, and renal injury. Treated hypertension may be associated with a pro-inflammatory gene signature in monocytes. Altered monocyte function, as reflected by altered gene expression, may contribute to the residual cardiovascular risk in patients with hypertension.

**[0080]** Monocytes are a type of white blood cell. Monocytes are part of the innate immune system of vertebrates and have multiple roles in immune function. Monocytes are produced by the bone marrow from precursors called monoblasts, which are bipotent cells that differentiated from hematopoietic stem cells. Monocytes circulate in the bloodstream for about one to three days and then typically move into tissues throughout the body. Circulating monocytes are pluripotent cells capable of differentiating into dendritic cells, macrophages, and microglial cells based on environmental cues. Monocytes can also present antigen without changing phenotype. Monocytes from hypertensive patients who are either untreated or have temporarily stopped treatment secrete more pro-inflammatory cytokines, such as, for example, interleukin  $1\beta$  and IL- $1\beta$ . Monocytes from these patients demonstrate enhanced migration, exhibit increased adherence to endothelial cells, and produce more reactive oxygen species. Monocytes from treated hypertensive patients exhibit higher levels of isoketals, which are a marker of oxidative stress and may adduct to proteins leading to the formation of neo-antigens.

**[0081]** Therapies may include anti-inflammatory therapy. Anti-inflammatory therapies, which may also be referred to as anti-inflammation treatments, may include the use of IL-1beta inhibitors, IL-18 inhibitors, IL-1b receptor antagonists, T-cell co-stimulation blockers, monoclonal antibodies to cytokines such as TNFalpha and IL-17A, IL-17RA monoclonal antibodies, inhibitors of interferon gamma (IFN $\gamma$ ), and combinations thereof. Examples of IL-1beta inhibitors include, for example, canakinumab and gevokizumab. Examples of IL-18 inhibitors include, for example, GSK-1070806 (monoclonal antibody that binds IL-18) and tadekinig alkfa (recombinant IL-18 binding protein). Examples of IL-1b receptor antagonists include, for example, anakinra. Examples of T-cell co-stimulation blockers include, for example, abatacept. Examples of monoclonal antibodies to TNFalpha include, for example, etanercept. Examples of monoclonal antibodies to IL-17A include, for example, secukinumab. Examples of IL-17RA monoclonal antibodies include, for example, brodalumab.

### 3. Biomarkers

**[0082]** The methods detailed herein include detecting and/or measuring the level of one or more biomarkers in a sample. A change or difference in the level of the biomarker in the sample obtained from the subject relative to a reference level indicates the subject is suffering from or is at risk of suffering from the disease. In some embodiments, the change or difference in the level of the biomarker may be an increase relative to the reference level. Such an increase in the level of the biomarker may indicate that the subject is suffering from or is at risk of suffering from the disease. In some embodiments, the change or difference in the level of the biomarker may be a decrease relative to the reference level. Such a decrease in the level of the biomarker may indicate that the subject is suffering from or is at risk of suffering from the disease. In some embodiments, the biomarker includes one or more of the biomarkers listed in **TABLE 3**. In some embodiments, the biomarker includes one or more of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, or VSIG4, or any combination thereof. In some embodiments, the biomarker includes one or more of IL18RAP, PGLYRP1, GZMH, ARG1, MMP8, or VSIG4, or any combination thereof. In some embodiments, the biomarker includes one or more of IL18RAP, LTF, or PGLYRP1, or any combination thereof. In some embodiments, the biomarker includes IL18RAP, or PGLYRP1, or a combination thereof. In some embodiments, the biomarker includes IL18RAP, or LTF, or a combination thereof. In some embodiments, the biomarker includes IL18RAP.

**a. IL18RAP**

**[0083]** Interleukin 18 receptor accessory protein (IL18RAP, also known as CD1218b; ACPL; CD218b; IL-1R7, IL18RB; CDw218b, IL-1R-7, IL-18RAcP; IL-1RAcPL; IL-18Rbeta; or IL-18R-beta) is an accessory subunit of the heterodimeric receptor for IL18. IL18RAP enhances the IL18 binding activity of IL18R1, which is a ligand binding subunit of IL18 receptor. The coexpression of IL18R1 and IL18RAP may be required for the activation of NF- $\kappa$ B and MAPK8 (JNK) in response to IL18.

**[0084]** In some embodiments, the biomarker includes IL18RAP. SEQ ID NO: 1 corresponds to the genomic polynucleotide sequence encoding the IL18RAP biomarker. In some embodiments, the IL18RAP biomarker is a IL18RAP polypeptide encoded by a polynucleotide of SEQ ID NO: 1 or a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the IL18RAP biomarker is a IL18RAP polynucleotide of SEQ ID NO: 1 or a complement thereof, a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the IL18RAP biomarker comprises a IL18RAP polypeptide comprising an amino acid sequence of SEQ ID NO: 8, a fragment thereof, a splice variant thereof, or a combination thereof.

**[0085]** An increase in the level of IL18RAP relative to the reference level may indicate that the subject is suffering from or is at risk of suffering from the disease. An increase in the level of IL18RAP relative to a control or reference level may indicate that the subject has or is at risk of having hypertension, or inflammation, or a combination thereof. The level of IL18RAP in the subject may be at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 4.5-fold, at least about 5-fold, at least about 5.5-fold, at least about 6-fold, at least about 6.5-fold, at least about 7-fold, at least about 7.5-fold, at least about 8-fold, at least about 8.5-fold, at least about 9-fold, at least about 9.5-fold, at least about 10-fold, at least about 10.5-fold, at least about 11-fold, at least about 11.5-fold, at least about 12-fold, at least about 12.5-fold, at least about 13-fold, at least about 13.5-fold, at least about 14-fold, at least about 14.5-fold, or at least about 15-fold greater than a control or reference level. The level of IL18RAP in the subject may be less than about 10-fold, less than about 9.5-fold, less than about 9-fold, less than about 8.5-fold, less than about 8-fold, less than about 7.5-fold, less than about 7-fold, less than about 6.5-fold, less than about 6-fold, less than about 5.5-fold, or less than about 5-fold greater than a control or reference level.

**b. LTF**

**[0086]** Lactotransferrin (LTF, also known as lactoferrin) is a globular glycoprotein and one of the components of the immune system. LTF sequesters free iron, transfers iron to cells, and controls the level of free iron in the blood and external secretions. LTF can exist in different polymeric forms ranging from monomers to tetramers in both in blood plasma and in secretory fluids.

**[0087]** In some embodiments, the biomarker includes LTF. SEQ ID NO: 2 corresponds to the genomic polynucleotide sequence encoding the LTF biomarker. In some embodiments, the LTF biomarker is a LTF polypeptide encoded by a polynucleotide of SEQ ID NO: 2 or a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the LTF biomarker is a LTF polynucleotide of SEQ ID NO: 2 or a complement thereof, a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the LTF biomarker comprises a LTF polypeptide comprising an amino acid sequence of SEQ ID NO: 9, a fragment thereof, a splice variant thereof, or a combination thereof.

**[0088]** An increase in the level of LTF relative to the reference level may indicate that the subject is suffering from or is at risk of suffering from the disease. An increase in the level of LTF relative to a control or reference level may indicate that the subject has or is at risk of having hypertension, or inflammation, or a combination thereof. The level of LTF in the subject may be at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 4.5-fold, at least about 5-fold, at least about 5.5-fold, at least about 6-fold, at least about 6.5-fold, at least about 7-fold, at least about 7.5-fold, at least about 8-fold, at least about 8.5-fold, at least about 9-fold, at least about 9.5-fold, at least about 10-fold, at least about 10.5-fold, at least about 11-fold, at least about 11.5-fold, at least about 12-fold, at least about 12.5-fold, at least about 13-fold, at least about 13.5-fold, at least about 14-fold, at least about 14.5-fold, or at least about 15-fold greater than a control or reference level. The level of LTF in the subject may be less than about 10-fold, less than about 9.5-fold, less than about 9-fold, less than about 8.5-fold, less than about 8-fold, less than about 7.5-fold, less than about 7-fold, less than about 6.5-fold, less than about 6-fold, less than about 5.5-fold, or less than about 5-fold greater than a control or reference level.

**c. PGLYRP1**

**[0089]** Peptidoglycan recognition protein (PGLYRP1) is a pathogen recognition protein with antimicrobial properties and is suspected to play an important role in maintaining the gut microbial flora. PGLYRP-1 is highly expressed in bone marrow, circulating polymorphonuclear leukocytes (PMLs), and in the corneal epithelium. PGLYRP1 may form homodimers for its antimicrobial activity and may complex with HSP70 for its cytotoxic activity.

**[0090]** In some embodiments, the biomarker includes PGLYRP1. SEQ ID NO: 3 corresponds to the genomic polynucleotide sequence encoding the PGLYRP1 biomarker. In some embodiments, the PGLYRP1 biomarker is a PGLYRP1 polypeptide encoded by a polynucleotide of SEQ ID NO: 3 or a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the PGLYRP1 biomarker is a PGLYRP1 polynucleotide of SEQ ID NO: 3 or a complement thereof, a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the PGLYRP1 biomarker comprises a PGLYRP1 polypeptide comprising an amino acid sequence of SEQ ID NO: 10, a fragment thereof, a splice variant thereof, or a combination thereof.

**[0091]** An increase in the level of PGLYRP1 relative to the reference level may indicate that the subject is suffering from or is at risk of suffering from the disease. An increase in the level of PGLYRP1 relative to a control or reference level may indicate that the subject has or is at risk of having hypertension, or inflammation, or a combination thereof. The level of PGLYRP1 in the subject may be at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 4.5-fold, at least about 5-fold, at least about 5.5-fold, at least about 6-fold, at least about 6.5-fold, at least about 7-fold, at least about 7.5-fold, at least about 8-fold, at least about 8.5-fold, at least about 9-fold, at least about 9.5-fold, at least about 10-fold, at least about 10.5-fold, at least about 11-fold, at least about 11.5-fold, at least about 12-fold, at least about 12.5-fold, at least about 13-fold, at least about 13.5-fold, at least about 14-fold, at least about 14.5-fold, or at least about 15-fold greater than a control or reference level. The level of PGLYRP1 in the subject may be less than about 10-fold, less than about 9.5-fold, less than about 9-fold, less than about 8.5-fold, less than about 8-fold, less than about 7.5-fold, less than about 7-fold, less than about 6.5-fold, less than about 6-fold, less than about 5.5-fold, or less than about 5-fold greater than a control or reference level.

**d. GZMH**

**[0092]** Granzyme H (GZMH) is a protein also known as cathepsin G-like 2 and protein h-CCPX. GZMH is a member of the peptidase S1 family of serine proteases. GZMH may be expressed in the NK (natural killer) cells of the immune system and may play a role in the cytotoxic arm of the innate immune response by inducing target cell death and directly cleaving substrates in pathogen-infected cells.

**[0093]** In some embodiments, the biomarker includes GZMH. SEQ ID NO: 4 corresponds to the genomic polynucleotide sequence encoding the GZMH biomarker. In some embodiments, the GZMH biomarker is a GZMH polypeptide encoded by a polynucleotide of SEQ ID NO: 4 or a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the GZMH biomarker is a GZMH polynucleotide of SEQ ID NO: 4 or a complement thereof, a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the GZMH biomarker comprises a GZMH polypeptide comprising an amino acid sequence of SEQ ID NO: 11, a fragment thereof, a splice variant thereof, or a combination thereof.

**[0094]** An increase in the level of GZMH relative to the reference level may indicate that the subject is suffering from or is at risk of suffering from the disease. An increase in the level of GZMH relative to a control or reference level may indicate that the subject has or is at risk of having hypertension, or inflammation, or a combination thereof. The level of GZMH in the subject may be at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 4.5-fold, at least about 5-fold, at least about 5.5-fold, at least about 6-fold, at least about 6.5-fold, at least about 7-fold, at least about 7.5-fold, at least about 8-fold, at least about 8.5-fold, at least about 9-fold, at least about 9.5-fold, at least about 10-fold, at least about 10.5-fold, at least about 11-fold, at least about 11.5-fold, at least about 12-fold, at least about 12.5-fold, at least about 13-fold, at least about 13.5-fold, at least about 14-fold, at least about 14.5-fold, or at least about 15-fold greater than a control or reference level. The level of GZMH in the subject may be less than about 10-fold, less than about 9.5-fold, less than about 9-fold, less than about 8.5-fold, less than about 8-fold, less than about 7.5-fold, less than about 7-fold, less than about 6.5-fold, less than about 6-fold, less than about 5.5-fold, or less than about 5-fold greater than a control or reference level.

**e. ARG1**

**[0095]** Arginase 1 (ARG1) is a protein that catalyzes the hydrolysis of arginine to ornithine and urea. At least two isoforms of mammalian arginase exist (types I and II), which differ in their tissue distribution, subcellular localization, immunologic crossreactivity, and physiologic function. ARG1 is a cytosolic enzyme and expressed predominantly in the liver as a component of the urea cycle.

**[0096]** In some embodiments, the biomarker includes ARG1. SEQ ID NO: 5 corresponds to the genomic polynucleotide sequence encoding the ARG1 biomarker. In some embodiments, the ARG1 biomarker is a ARG1 polypeptide encoded by a polynucleotide of SEQ ID NO: 5 or a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the ARG1 biomarker is a ARG1 polynucleotide of SEQ ID NO: 5 or a complement thereof, a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the ARG1 biomarker comprises a ARG1 polypeptide comprising an amino acid sequence of SEQ ID NO: 12, a fragment thereof, a splice variant thereof, or a combination thereof.

**[0097]** An increase in the level of ARG1 relative to the reference level may indicate that the subject is suffering from or is at risk of suffering from the disease. An increase in the level of ARG1 relative to a control or reference level may indicate that the subject has or is at risk of having hypertension, or inflammation, or a combination thereof. The level of ARG1 in the subject may be at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 4.5-fold, at least about 5-fold, at least about 5.5-fold, at least about 6-fold, at least about 6.5-fold, at least about 7-fold, at least about 7.5-fold, at least about 8-fold, at least about 8.5-fold, at least about 9-fold, at least about 9.5-fold, at least about 10-fold, at least about 10.5-fold, at least about 11-fold, at least about 11.5-fold, at least about 12-fold, at least about 12.5-fold, at least about 13-fold, at least about 13.5-fold, at least about 14-fold, at least about 14.5-fold, or at least about 15-fold greater than a control or reference level. The level of ARG1 in the subject may be less than about 10-fold, less than about 9.5-fold, less than about 9-fold, less than about 8.5-fold, less than about 8-fold, less than about 7.5-fold, less than about 7-fold, less than about 6.5-fold, less than about 6-fold, less than about 5.5-fold, or less than about 5-fold greater than a control or reference level.

**f. MMP8**

**[0098]** Matrix metalloproteinase-8 (MMP8, also known as neutrophil collagenase or PMNL collagenase) is a collagen cleaving enzyme, and more specifically, its function is the degradation of type I, type II, and type III collagens. MMP8 is a member of the matrix metalloproteinase (MMP) family, which are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes such as arthritis and metastasis. MMP8 is present in the connective tissue of most mammals. MMP8 is stored in secondary granules within neutrophils and is activated by autolytic cleavage.

**[0099]** In some embodiments, the biomarker includes MMP8. SEQ ID NO: 6 corresponds to the genomic polynucleotide sequence encoding the MMP8 biomarker. In some embodiments, the MMP8 biomarker is a MMP8 polypeptide encoded by a polynucleotide of SEQ ID NO: 6 or a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the MMP8 biomarker is a MMP8 polynucleotide of SEQ ID NO: 6 or a complement thereof, a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the MMP8 biomarker comprises a MMP8 polypeptide comprising an amino acid sequence of SEQ ID NO: 13, a fragment thereof, a splice variant thereof, or a combination thereof.

**[00100]** An increase in the level of MMP8 relative to the reference level may indicate that the subject is suffering from or is at risk of suffering from the disease. An increase in the level of MMP8 relative to a control or reference level may indicate that the subject has or is at risk of having hypertension, or inflammation, or a combination thereof. The level of MMP8 in the subject may be at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 4.5-fold, at least about 5-fold, at least about 5.5-fold, at least about 6-fold, at least about 6.5-fold, at least about 7-fold, at least about 7.5-fold, at least about 8-fold, at least about 8.5-fold, at least about 9-fold, at least about 9.5-fold, at least about 10-fold, at least about 10.5-fold, at least about 11-fold, at least about 11.5-fold, at least about 12-fold, at least about 12.5-fold, at least about 13-fold, at least about 13.5-fold, at least about 14-fold, at least about 14.5-fold, or at least about 15-fold greater than a control or reference level. The level of MMP8 in the subject may be less than about 10-fold, less than about 9.5-fold, less than about 9-fold, less than about 8.5-fold, less than about 8-fold, less than about 7.5-fold, less than about 7-fold, less than about 6.5-fold, less than about 6-fold, less than about 5.5-fold, or less than about 5-fold greater than a control or reference level.

#### g. VSIG4

**[00101]** V-set and immunoglobulin domain containing 4 (VSIG4) is a protein that is structurally related to the B7 family of immune regulatory proteins. VSIG4 may be a negative regulator of T-cell responses. VSIG4 is also a receptor for the complement component 3 fragments C3b and iC3b.

**[00102]** In some embodiments, the biomarker includes VSIG4. SEQ ID NO: 7 corresponds to the genomic polynucleotide sequence encoding the VSIG4 biomarker. In some embodiments, the VSIG4 biomarker is a VSIG4 polypeptide encoded by a polynucleotide of SEQ ID NO: 7 or a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the VSIG4 biomarker is a VSIG4 polynucleotide of SEQ ID NO: 7 or a complement thereof, a fragment thereof, a splice variant thereof, or a combination thereof. In some embodiments, the VSIG4 biomarker comprises a VSIG4 polypeptide comprising an amino acid sequence of SEQ ID NO: 14, a fragment thereof, a splice variant thereof, or a combination thereof.

**[00103]** A decrease in the levels of VSIG4 relative to the reference level may indicate that the subject is suffering from or is at risk of suffering from the disease. A decrease in the level of VSIG4 relative to a control or reference level may indicate that the subject has or is at risk of having hypertension, or inflammation, or a combination thereof. The level of VSIG4 in the subject may be at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 4.5-fold, or at least about 5-fold less than a control or reference level. The level of VSIG4 in the subject may be less than about 10%, less than about 15%, less than about 20%, less than about 25%, less than about 30%, less than about 35%, less than about 40%, less than about 45%, less than about 50%, less than about 55%, less than about 60%, less than about 65%, less than about 70%, or less than about 75% of the level in a control or reference level.

#### 4. Determining The Level Of A Biomarker

**[00104]** The presence or level of the biomarker in a sample may be determined or detected by any method known by one of skill in the art. For example, the biomarker may be detected and/or quantified by employing an immunoassay, Northern blot analysis, Southern blot analysis, Western blot analysis, sequencing, RNA-sequencing, PCR, reverse-transcriptase PCR, a hybridization assay such as *in situ* hybridization such as FISH, RNA flow cytometry, mass cytometry time of flight (CyTOF), or a combination thereof.

### a. Hybridization Assays

[00105] In some embodiments, one or more biomarkers is detected and/or quantified in a sample using *in situ* hybridization. The methods are typically carried out on a sample of cells that are fresh, frozen, fixed, and/or treated to, for example, increase accessibility of target polynucleotide or reduce non-specific binding. A sample may be subjected to hybridization with one or more probes, washing to remove any unbound probes, and detection of hybridized probes.

[00106] Provided herein are compositions including a probe array for detecting one or more biomarkers in a sample. In some embodiments, the array includes a plurality of probes that hybridizes to one or more biomarkers. In some embodiments, the composition further includes a solid support with the plurality of probes attached thereto.

[00107] In some embodiments, probes are detectably labeled, and each probe is distinctly labeled. In some embodiments, the probes are detectably labeled with fluorophores, and each probe is distinctly labeled. Attachment of fluorophores to nucleic acid probes is well-known in the art and can be accomplished by any available means.

[00108] One of skill in the art will recognize that other agents or dyes can be used in lieu of fluorophores as label-containing moieties. Luminescent agents include, for example, radioluminescent, chemiluminescent, bioluminescent, and phosphorescent label containing moieties. Alternatively, detection moieties that are visualized by indirect means can be used. For example, probes can be labeled with biotin or digoxigenin using routine methods known in the art, and then further processed for detection. Visualization of a biotin-containing probe can be achieved via subsequent binding of avidin conjugated to a detectable marker.

### b. Immunoassay

[00109] The presence or amount of biomarker can be determined using antibodies that specifically bind to each biomarker (e.g., IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, or VSIG4, as well as any additional analytes if such additional analytes are used). Examples of antibodies that can be used include a polyclonal antibody, a monoclonal antibody, a human antibody, an immunoglobulin molecule, a disulfide linked Fv, a monoclonal antibody, an affinity matured, a scFv, a chimeric antibody, a single domain antibody, a CDR-grafted antibody, a diabody, a humanized antibody, a multi-specific antibody, a Fab, a dual specific antibody, a DVD, a Fab', a bispecific antibody, a F(ab')<sub>2</sub>, a Fv, and combinations thereof.

**[00110]** Any immunoassay may be utilized. The immunoassay may be an enzyme-linked immunoassay (ELISA), radioimmunoassay (RIA), a competitive inhibition assay, such as forward or reverse competitive inhibition assays, a fluorescence polarization assay, or a competitive binding assay, for example. The ELISA may be a sandwich ELISA. Specific immunological binding of the antibody to the marker can be detected via direct labels, such as fluorescent or luminescent tags, metals and radionuclides attached to the antibody or via indirect labels, such as alkaline phosphatase or horseradish peroxidase.

**[00111]** The use of immobilized antibodies or fragments thereof may be incorporated into the immunoassay. The antibodies may be immobilized onto a variety of supports, such as magnetic or chromatographic matrix particles, the surface of an assay plate (such as microtiter wells), pieces of a solid substrate material, and the like. An assay strip can be prepared by coating the antibody or plurality of antibodies in an array on a solid support. This strip can then be dipped into the test biological sample and then processed quickly through washes and detection steps to generate a measurable signal, such as a colored spot.

**[00112]** The sandwich ELISA measures the amount of antigen between two layers of antibodies (i.e., a capture antibody and a detection antibody, which may be labeled with a detectable label). The biomarker to be measured may contain at least two antigenic sites capable of binding to antibody. Either monoclonal or polyclonal antibodies may be used as the capture and detection antibodies in the sandwich ELISA.

**[00113]** Generally, at least two antibodies are employed to separate and quantify the biomarker in a test or biological sample. More specifically, the at least two antibodies bind to certain epitopes of the biomarker forming an immune complex which is referred to as a "sandwich". One or more antibodies can be used to capture the biomarker in the test sample (these antibodies are frequently referred to as a "capture" antibody or "capture" antibodies) and one or more antibodies is used to bind a detectable (namely, quantifiable) label to the sandwich (these antibodies are frequently referred to as the "detection" antibody or "detection" antibodies). In a sandwich assay, both antibodies binding to their epitope may not be diminished by the binding of any other antibody in the assay to its respective epitope. In other words, antibodies may be selected so that the one or more first antibodies brought into contact with a test sample suspected of containing biomarker do not bind to all or part of an epitope recognized by the second or subsequent antibodies, thereby interfering with the ability of the one or more second detection antibodies to bind to the biomarker.

**[00114]** In some embodiments, a test or biological sample suspected of containing a biomarker can be contacted with at least one first capture antibody (or antibodies) and at least one second detection antibodies either simultaneously or sequentially. In the sandwich assay format, a test sample suspected of containing a biomarker is first brought into contact with the at least one first capture antibody that specifically binds to a particular epitope under conditions which allow the formation of a first antibody-biomarker complex. If more than one capture antibody is used, a first multiple capture antibody-biomarker complex is formed. In a sandwich assay, the antibodies, preferably, the at least one capture antibody, are used in molar excess amounts of the maximum amount of the biomarker expected in the test sample.

**[00115]** Optionally, prior to contacting the test sample with the at least one first capture antibody, the at least one first capture antibody can be bound to a solid support which facilitates the separation of the first antibody-biomarker complex from the test sample. Any solid support known in the art can be used, including but not limited to, solid supports made out of polymeric materials in the forms of wells, tubes, or beads. The antibody (or antibodies) can be bound to the solid support by adsorption, by covalent bonding using a chemical coupling agent, or by other means known in the art, provided that such binding does not interfere with the ability of the antibody to bind the marker. Moreover, if necessary, the solid support can be derivatized to allow reactivity with various functional groups on the antibody. Such derivatization requires the use of certain coupling agents such as, but not limited to, maleic anhydride, N-hydroxysuccinimide and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

**[00116]** After the test sample suspected of containing a biomarker is brought into contact with the at least one first capture antibody, the test sample is incubated in order to allow for the formation of a first capture antibody (or multiple antibody)-biomarker complex. The incubation can be carried out at a pH of from about 4.5 to about 10.0, at a temperature of from about 2°C to about 45°C, and for a period from at least about one (1) minute to about eighteen (18) hours, from about 2-6 minutes, or from about 3-4 minutes.

**[00117]** After formation of the first/multiple capture antibody-biomarker complex, the complex is then contacted with at least one second detection antibody (under conditions which allow for the formation of a first/multiple antibody-biomarker-second antibody complex). If the first antibody-biomarker complex is contacted with more than one detection antibody, then a first/multiple capture antibody-biomarker multiple antibody detection complex is formed. As with first antibody, when the at least second (and subsequent) antibody is brought into contact with the first antibody-biomarker complex, a period of

incubation under conditions similar to those described above is required for the formation of the first/multiple antibody-biomarker/multiple antibody complex. Preferably, at least one second antibody contains a detectable label. The detectable label can be bound to the at least one second antibody prior to, simultaneously with, or after the formation of the first/multiple antibody-biomarker/multiple antibody complex. Any detectable label known in the art can be used.

## **5. Modulating The Level Of A Biomarker**

**[00118]** The level of a biomarker in a subject may be modulated to treat a subject. The level of a biomarker in a subject may be modulated by any suitable method known by one of skill in the art. The transcription, expression, or activity of, or a combination thereof, a gene or gene product of a biomarker may be inhibited. The level of a biomarker may be decreased by administering an inhibitor. Inhibitors may include a small molecule, polynucleotide such as interfering RNA, polypeptide such as an antibody, carbohydrate, lipid, or a combination thereof. In some embodiments, the level of at least one of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof, is decreased to treat a subject. In some embodiments, the level of at least one of IL18RAP, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof, is decreased to treat a subject. In some embodiments, the level of IL18RAP, or PGLYRP1, or a combination thereof, is decreased to treat a subject. The level of the biomarker may be decreased by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, relative to a control.

**[00119]** The transcription, expression, or activity of, or a combination thereof, a gene or gene product of a biomarker may be increased or enhanced. The level of a biomarker may be increased by administering an agonist. Agonists may include a small molecule, polynucleotide, polypeptide, carbohydrate, lipid, or a combination thereof. For example, agonists may include transcription activators, small molecule agonists, or the polypeptide gene product of the biomarker itself. In some embodiments, the level of VSIG4 is increased to treat a subject. The level of the biomarker may be increased by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at

least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, relative to a control.

**[00120]** Agents that modulate the level of a biomarker may be administered to a subject. Agents that modulate the level of a biomarker can be formulated into a composition and administered in dosages and by techniques well known to those skilled in the medical arts taking into consideration such factors as the age, sex, weight, and condition of the particular subject, and the route of administration.

**[00121]** Agents that modulate the level of a biomarker can be administered prophylactically or therapeutically. In prophylactic administration, agents can be administered in an amount sufficient to induce a response. In therapeutic applications, agents are administered to a subject in need thereof in an amount sufficient to elicit a therapeutic effect. Agents may be administered in a therapeutically effective amount.

**[00122]** Agents that modulate the level of a biomarker can be administered by methods well known in the art as described in Donnelly et al. (*Ann. Rev. Immunol.* **1997**, *15*, 617-648); Felgner et al. (U.S. Patent No. 5,580,859, issued Dec. 3, 1996); Felgner (U.S. Patent No. 5,703,055, issued Dec. 30, 1997); and Carson et al. (U.S. Patent No. 5,679,647, issued Oct. 21, 1997), the contents of all of which are incorporated herein by reference in their entirety. The agents can be complexed to particles or beads that can be administered to an individual, for example, using a vaccine gun. One skilled in the art would know that the choice of a pharmaceutically acceptable carrier, including a physiologically acceptable compound, depends, for example, on the route of administration.

**[00123]** Agents that modulate the level of a biomarker can be delivered via a variety of routes. Typical delivery routes may include parenteral administration, e.g., intradermal, intramuscular or subcutaneous delivery. Other routes may include oral administration, intranasal, intravaginal, transdermal, intravenous, intraarterial, intratumoral, intraperitoneal, and epidermal routes. In some embodiments, the agent is administered intravenously, intraarterially, or intraperitoneally to the subject.

**[00124]** Agents that modulate the level of a biomarker can be a liquid preparation such as a suspension, syrup, or elixir. The agent can be incorporated into liposomes, microspheres, or other polymer matrices (such as by a method described in Felgner et al., U.S. Patent No. 5,703,055; Gregoriadis, *Liposome Technology*, Vols. I to III (2nd ed. 1993), the contents of which are incorporated herein by reference in their entirety). Liposomes can consist of

phospholipids or other lipids, and can be nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

**[00125]** Agents that modulate the level of a biomarker may be used as a vaccine. The vaccine can be administered via electroporation, such as by a method described in U.S. Patent No. 7,664,545, the contents of which are incorporated herein by reference. The electroporation can be by a method and/or apparatus described in U.S. Patent Nos. 6,302,874; 5,676,646; 6,241,701; 6,233,482; 6,216,034; 6,208,893; 6,192,270; 6,181,964; 6,150,148; 6,120,493; 6,096,020; 6,068,650; and 5,702,359, the contents of which are incorporated herein by reference in their entirety. The electroporation can be carried out via a minimally invasive device.

**[00126]** In some embodiments, an agent that modulates the level of a biomarker is administered in a controlled release formulation. The agent may be released into the circulation, for example. In some embodiments, the agent may be released over a period of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 7 days, at least about 1 week, at least about 1.5 weeks, at least about 2 weeks, at least about 2.5 weeks, at least about 3.5 weeks, at least about 4 weeks, or at least about 1 month.

## **6. Methods**

### **a. Methods Of Diagnosing A Disease**

**[00127]** Provided herein is a method of diagnosing a disease, such as hypertension, or inflammation in a subject being treated for hypertension. The method may include obtaining a sample from the subject, determining a level of a biomarker in the sample, and comparing the level of the biomarker to a reference level of the biomarker. The methods may further include identifying the subject as having the disease when the level of the biomarker is different from the reference level of the biomarker.

**[00128]** Provided herein is a method of diagnosing and treating a disease, such as hypertension, or inflammation in a subject being treated for hypertension. The method may include obtaining a sample from the subject, determining a level of a biomarker in the sample, and comparing the level of the biomarker to a reference level of the biomarker. The methods may further include identifying the subject as having the disease when the level of the biomarker is different from the reference level of the biomarker.

**[00129]** In some embodiments, the methods may further include determining the level of at least one additional biomarker in the sample. The at least one additional biomarker may be selected from the other of the biomarkers listed in **TABLE 3**. In some embodiments, the at least one additional biomarker may be selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4. In some embodiments, the methods may further include comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker. The methods may further include identifying the subject as having the disease when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker.

**[00130]** In some embodiments, the subject is identified as having the disease when the level of IL18RAP in the sample is greater than the reference level of IL18RAP. In some embodiments, the subject is identified as having the disease when the level of LTF in the sample is greater than the reference level of LTF. In some embodiments, the subject is identified as having the disease when the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1. In some embodiments, the subject is identified as having the disease when the level of GZMH in the sample is greater than the reference level of GZMH. In some embodiments, the subject is identified as having the disease when the level of ARG1 in the sample is greater than the reference level of ARG1. In some embodiments, the subject is identified as having the disease when the level of MMP8 in the sample is greater than the reference level of MMP8. In some embodiments, the subject is identified as having the disease when the level of VSIG4 in the sample is less than the reference level of VSIG4.

**[00131]** In some embodiments, the methods further include administering a therapy to the subject diagnosed with or identified as having the disease. The disease may include hypertension, or inflammation, or a combination thereof.

**b. Methods Of Determining If A Subject Being Treated For Hypertension Has Or Is At Risk Of Developing Inflammation**

**[00132]** Provided herein is a method of determining if a subject being treated for hypertension has or is at risk of developing inflammation. The methods may include obtaining a sample from the subject, determining a level of a biomarker in the sample, and comparing the level of the biomarker to a reference level of the biomarker. The methods may further include determining the subject has or is at risk of developing inflammation when the level of the biomarker is different from the reference level of the biomarker.

**[00133]** In some embodiments, the methods may further include determining the level of at least one additional biomarker in the sample. The at least one additional biomarker may be selected from the other of the biomarkers listed in **TABLE 3**. In some embodiments, the at least one additional biomarker may be selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4. In some embodiments, the methods may further include comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker. The methods may further include identifying the subject as having or is at risk of developing inflammation when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker.

**[00134]** In some embodiments, the subject is identified as having inflammation when the level of IL18RAP in the sample is greater than the reference level of IL18RAP. In some embodiments, the subject is identified as having inflammation when the level of LTF in the sample is greater than the reference level of LTF. In some embodiments, the subject is identified as having inflammation when the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1. In some embodiments, the subject is identified as having inflammation when the level of GZMH in the sample is greater than the reference level of GZMH. In some embodiments, the subject is identified as having inflammation when the level of ARG1 in the sample is greater than the reference level of ARG1. In some embodiments, the subject is identified as having inflammation when the level of MMP8 in the sample is greater than the reference level of MMP8. In some embodiments, the subject is identified as having inflammation when the level of VSIG4 in the sample is less than the reference level of VSIG4.

**[00135]** In some embodiments, the methods further include administering a therapy to the subject diagnosed with inflammation or identified as having inflammation or is at risk of developing inflammation.

**c. Methods Of Monitoring Progression Of Inflammation In A Subject Being Treated For Hypertension**

**[00136]** Provided herein is a method of monitoring progression of inflammation in a subject being treated for hypertension. The methods may include obtaining first and second samples from the subject, determining a first level of a biomarker in the first sample and a second level of the biomarker in the second sample, and comparing the first and second levels of the biomarker. The methods may further include determining that inflammation has progressed in the subject when the second level of the biomarker is different from the first

level of the biomarker, or inflammation has not progressed in the subject when the second level of the biomarker is equivalent to the first level of the biomarker. In some embodiments, the methods may include determining that (i) inflammation has progressed in the subject when the second level of the biomarker is greater than the first level of the biomarker, or inflammation has not progressed in the subject when the second level of the biomarker is equivalent to or less than the first level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8; or that (ii) inflammation has progressed in the subject when the second level of the biomarker is less than the first level of the biomarker, or inflammation has not progressed in the subject when the second level of the biomarker is equivalent to or greater than the first level of the biomarker, wherein the biomarker is VSIG4.

**[00137]** In some embodiments, the methods may further include determining a first level of at least one additional biomarker in the first sample and a second level of the at least one additional biomarker in the second sample. The at least one additional biomarker may be selected from the other of the biomarkers listed in **TABLE 3**. In some embodiments, the at least one additional biomarker may be selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4. In some embodiments, the methods may further include comparing the first and second levels of the at least one additional biomarker. In some embodiments, the methods further include determining that inflammation has progressed in the subject when the second level of the additional biomarker is different from the first level of the additional biomarker. In some embodiments, the methods include determining that (i) inflammation has progressed in the subject when the second level of the additional biomarker is greater than the first level of the additional biomarker, or inflammation has not progressed in the subject when the second level of the additional biomarker is equivalent to or less than the first level of the additional biomarker, wherein the additional biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or that (ii) inflammation has progressed in the subject when the second level of the additional biomarker is less than the first level of the additional biomarker, or inflammation has not progressed in the subject when the second level of the additional biomarker is equivalent to or greater than the first level of the additional biomarker, wherein the additional biomarker is VSIG4.

**[00138]** The first biological sample may be obtained from the subject before or prior to the second biological sample is obtained from the subject. The first biological sample may be obtained from the subject at least about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27

days, 28 days, 29 days, 30 days, 31 days, 32 days, 33 days, 34 days, 35 days, 36 days, 37 days, 38 days, 39 days, 40 days, 41 days, 42 days, 43 days, 44 days, 45 days, 46 days, 47 days, 48 days, 49 days, 50 days, 51 days, 52 days, 53 days, 54 days, 55 days, 56 days, 57 days, 58 days, 59 days, 60 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, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, 1 month, 2 months, 3 months, 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, 24 months, 1 year, 2 years, 3 years, 4 years, or 5 years before the second biological sample is obtained from the subject.

**[00139]** In some embodiments, the methods further include administering a therapy to the subject when inflammation has progressed in the subject.

**d. Methods Of Determining If A Subject Being Treated For Hypertension Would Benefit From Anti-Inflammatory Therapy**

**[00140]** Provided herein are methods of determining if a subject being treated for hypertension would benefit from anti-inflammatory therapy. The methods may include obtaining a sample from the subject, determining a level of a biomarker in the sample, and comparing the level of the biomarker to a reference level of the biomarker. The methods may further include determining that the subject would benefit from anti-inflammatory therapy when the level of the biomarker is different from the reference level of the biomarker.

**[00141]** In some embodiments, the methods may further include determining the level of at least one additional biomarker in the sample. The at least one additional biomarker may be selected from the other of the biomarkers listed in **TABLE 3**. In some embodiments, the at least one additional biomarker may be selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4. In some embodiments, the methods may further include comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker. In some embodiments, the methods further include determining that the subject would benefit from anti-inflammatory therapy when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker.

**[00142]** In some embodiments, the subject is determined to likely benefit from anti-inflammatory therapy when the level of IL18RAP in the sample is greater than the reference level of IL18RAP. In some embodiments, the subject is determined to likely benefit from anti-inflammatory therapy when the level of LTF in the sample is greater than the reference level of LTF. In some embodiments, the subject is determined to likely benefit from anti-inflammatory therapy when the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1. In some embodiments, the subject is determined to likely benefit from anti-inflammatory therapy when the level of GZMH in the sample is greater than the reference level of GZMH. In some embodiments, the subject is determined to likely benefit from anti-inflammatory therapy when the level of ARG1 in the sample is greater than the reference level of ARG1. In some embodiments, the subject is determined to likely benefit from anti-inflammatory therapy when the level of MMP8 in the sample is greater than the reference level of MMP8. In some embodiments, the subject is determined to likely benefit from anti-inflammatory therapy when the level of VSIG4 in the sample is less than the reference level of VSIG4.

**[00143]** In some embodiments, the methods further include administering anti-inflammatory therapy to the subject determined to likely benefit from anti-inflammatory therapy.

**e. Methods Of Monitoring A Subject's Response To Anti-Inflammatory Therapy,  
Wherein The Subject Is Being Co-Treated For Hypertension**

**[00144]** Provided herein are methods of monitoring a subject's response to anti-inflammatory therapy, wherein the subject is being co-treated for hypertension. The methods may include obtaining first and second samples from the subject, determining a first level of a biomarker in the first sample and a second level of the biomarker in the second sample, and comparing the first and second levels of the biomarker. The methods may further include determining that the subject is not responding to the anti-inflammatory therapy when the second level of the biomarker is different from the first level of the biomarker, or that the subject is responding to the anti-inflammatory therapy when the second level of the biomarker is equivalent to the first level of the biomarker. In some embodiments, the methods include determining that (i) the subject is not responding to the anti-inflammatory therapy when the second level of the biomarker is greater than the first level of the biomarker, or subject is responding to the anti-inflammatory therapy when the second level of the biomarker is equivalent to or less than the first level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or that (ii) the subject is not responding to the anti-inflammatory therapy when the

second level of the biomarker is less than the first level of the biomarker, or the subject is responding to the anti-inflammatory therapy when the second level of the biomarker is equivalent to or greater than the first level of the biomarker, wherein the biomarker is VSIG4.

**[00145]** In some embodiments, the methods may further include determining a first level of at least one additional biomarker in the first sample and a second level of the at least one additional biomarker in the second sample. The at least one additional biomarker may be selected from the other of the biomarkers listed in **TABLE 3**. In some embodiments, the at least one additional biomarker may be selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4. In some embodiments, the methods further include comparing the first and second levels of the at least one additional biomarker. In some embodiments, the methods include determining that (i) the subject is not responding to the anti-inflammatory therapy when the second level of the additional biomarker is greater than the first level of the additional biomarker, or the subject is responding to the anti-inflammatory therapy when the second level of the additional biomarker is equivalent to or less than the first level of the additional biomarker, wherein the additional biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8; or that (ii) the subject is not responding to the anti-inflammatory therapy when the second level of the additional biomarker is less than the first level of the additional biomarker, or the subject is responding to the anti-inflammatory therapy when the second level of the additional biomarker is equivalent to or greater than the first level of the additional biomarker, wherein the additional biomarker is VSIG4.

**[00146]** The first biological sample may be obtained from the subject prior to or before the second biological sample is obtained from the subject. The first biological sample may be obtained from the subject at least about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, 32 days, 33 days, 34 days, 35 days, 36 days, 37 days, 38 days, 39 days, 40 days, 41 days, 42 days, 43 days, 44 days, 45 days, 46 days, 47 days, 48 days, 49 days, 50 days, 51 days, 52 days, 53 days, 54 days, 55 days, 56 days, 57 days, 58 days, 59 days, 60 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, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48

weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, 1 month, 2 months, 3 months, 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, 24 months, 1 year, 2 years, 3 years, 4 years, or 5 years before the second biological sample is obtained from the subject.

**[00147]** In some embodiments, the methods further include administering or continuing to administer anti-inflammatory therapy to the subject who is responding to the anti-inflammatory therapy.

#### **f. Methods Of Diagnosing Hypertension In A Subject**

**[00148]** Provided herein are methods of diagnosing hypertension in a subject. The methods may include obtaining a sample from the subject, determining a level of a biomarker in the sample, and comparing the level of the biomarker to a reference level of the biomarker. In some embodiments, the methods further include identifying the subject as having hypertension when the level of the biomarker is different from the reference level of the biomarker.

**[00149]** Provided herein are methods of diagnosing and treating hypertension in a subject. The methods may include obtaining a sample from the subject, determining a level of a biomarker in the sample, and comparing the level of the biomarker to a reference level of the biomarker. In some embodiments, the methods further include identifying the subject as having hypertension when the level of the biomarker is different from the reference level of the biomarker.

**[00150]** In some embodiments, the methods may further include determining the level of at least one additional biomarker in the sample. The at least one additional biomarker may be selected from the other of the biomarkers listed in **TABLE 3**. In some embodiments, the at least one additional biomarker may be selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4. In some embodiments, the methods may further include comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker. The methods may further include identifying the subject as having hypertension when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker.

**[00151]** In some embodiments, the subject is identified as having hypertension when the level of IL18RAP in the sample is greater than the reference level of IL18RAP. In some embodiments, the subject is identified as having hypertension when the level of LTF in the

sample is greater than the reference level of LTF. In some embodiments, the subject is identified as having hypertension when the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1. In some embodiments, the subject is identified as having hypertension when the level of GZMH in the sample is greater than the reference level of GZMH. In some embodiments, the subject is identified as having hypertension when the level of ARG1 in the sample is greater than the reference level of ARG1. In some embodiments, the subject is identified as having hypertension when the level of MMP8 in the sample is greater than the reference level of MMP8. In some embodiments, the subject is identified as having hypertension when the level of VSIG4 in the sample is less than the reference level of VSIG4.

**[00152]** In some embodiments, the methods further include administering therapy to the subject identified as having hypertension.

#### **g. Method Of Treating Inflammation In A Subject Being Treated For Hypertension**

**[00153]** Provided herein are methods of treating inflammation in a subject being treated for hypertension. The methods may include inhibiting the transcription, expression, or activity of, or a combination thereof, a gene or gene product of a biomarker. The methods may include administering an inhibitor. In some embodiments, the methods include inhibiting the transcription, expression, or activity of, or a combination thereof, a gene or gene product of a biomarker selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof. In some embodiments, the methods include administering an inhibitor of a biomarker selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8. The methods may include increasing the transcription, expression, or activity, or a combination thereof, of a biomarker. The methods may include administering an agonist. In some embodiments, the methods include increasing the transcription, expression, or activity of a biomarker selected from VSIG4. In some embodiments, the methods include administering an agonist of a biomarker selected from VSIG4.

#### **h. Method Of Treating Hypertension In A Subject**

**[00154]** Provided herein are methods of treating hypertension in a subject. The methods may include inhibiting the transcription, expression, or activity of, or a combination thereof, a gene or gene product of a biomarker. The methods may include administering an inhibitor. In some embodiments, the methods include inhibiting the transcription, expression, or activity of, or a combination thereof, a gene or gene product of a biomarker selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, or a combination thereof. In some

embodiments, the methods include administering an inhibitor of a biomarker selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8. The methods may include increasing the transcription, expression, or activity of, or a combination thereof, a gene or gene product of a biomarker. The methods may include administering an agonist. In some embodiments, the methods include increasing the transcription, expression, or activity of, or a combination thereof, a gene or gene product of a biomarker selected from VSIG4. In some embodiments, the methods include administering an agonist of a biomarker selected from VSIG4.

## 7. Reference Level

**[00155]** The reference level may be a predetermined value or range, which is employed as a benchmark against which to assess the measured result. The terms "reference level," "reference," and "control" are used herein interchangeably. The predetermined level may be from a subject or a group. "Control group" as used herein refers to a group of control subjects. A control subject may be a healthy or normal subject or a subject having no clinical signs or symptoms of hypertension or inflammation or a combination thereof. In some embodiments, a control subject is a normotensive subject. The predetermined level may be a cutoff value from a control group. The predetermined level may be an average from a control group.

**[00156]** The amount or concentration of a biomarker may be "unchanged," "favorable" (or "favorably altered"), or "unfavorable" (or "unfavorably altered"). "Elevated" or "increased" refers to an amount or a concentration in a test sample that is greater than a reference level. The term "lowered" or "reduced" refers to an amount or a concentration in a test sample that is less than a reference level. The term "altered" refers to an amount or a concentration in a sample that is altered (increased or decreased) over a reference level.

**[00157]** In some embodiments, level of the biomarker is greater than the reference level of the biomarker when the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or combinations thereof. In some embodiments, level of the biomarker is less than the reference level of the biomarker when the biomarker is VSIG4.

**[00158]** Cutoff values (or predetermined cutoff values) may be determined by Adaptive Index Model (AIM) methodology. Cutoff values (or predetermined cutoff values) may be determined by a receiver operating curve (ROC) analysis from biological samples of the patient group. ROC analysis, as generally known in the biological arts, is a determination of the ability of a test to discriminate one condition from another, e.g., to determine the

performance of each marker in identifying a patient having disease. A description of ROC analysis as applied according to the present disclosure is provided in P.J. Heagerty et al. (Time-dependent ROC curves for censored survival data and a diagnostic marker, *Biometrics* 2000, 56, 337-44), the disclosure of which is hereby incorporated by reference in its entirety.

**[00159]** Alternatively, cutoff values can be determined by a quartile analysis of biological samples of a patient group. For example, a cutoff value can be determined by selecting a value that corresponds to any value in the 25th-75th percentile range, preferably a value that corresponds to the 25th percentile, the 50th percentile or the 75th percentile, and more preferably the 75th percentile.

**[00160]** Such statistical analyses can be performed using any method known in the art and can be implemented through any number of commercially available software packages (e.g., from Analyse-it Software Ltd., Leeds, UK; StataCorp LP, College Station, TX; SAS Institute Inc., Cary, NC.).

**[00161]** The healthy or normal levels or ranges for a biomarker are defined in accordance with standard practice.

## **8. Kit**

**[00162]** Also provided herein is a kit for use in performing the above-described methods. In some embodiments, the kit is for detecting hypertension in a subject. In some embodiments, the kit is for detecting inflammation in a subject being treated for hypertension. The kit may include instructions for detecting at least one biomarker. Instructions included in the kit may be affixed to packaging material or may be included as a package insert. The instructions may be written or printed materials, but are not limited to such. Any medium capable of storing such instructions and communicating them to an end user is contemplated by this disclosure. Such media include, but are not limited to, electronic storage media (e.g., magnetic discs, tapes, cartridges, chips), optical media (e.g., CD ROM), and the like. As used herein, the term "instructions" may include the address of an internet site that provides the instructions.

**[00163]** The kit may include one or more reagents for detecting a biomarker. In some embodiments, the kit includes one or more reagents for detecting a biomarker selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4. The kit may include reagents capable of specifically binding to each biomarker and/or to quantify the levels of the biomarker in a sample.

**[00164]** The kit may include a reference standard indicating reference levels of each of the biomarkers. The kit may include instructions for generating a standard curve or a reference standard for purposes of quantifying a biomarker.

**[00165]** Optionally, the kit includes quality control components (for example, sensitivity panels, calibrators, and positive controls). Preparation of quality control reagents is well-known in the art and is described on insert sheets for a variety of diagnostic products. Sensitivity panel members optionally are used to establish assay performance characteristics, and further optionally are useful indicators of the integrity of the kit reagents, and the standardization of assays.

**[00166]** The kit can also optionally include other reagents required to conduct a diagnostic assay or facilitate quality control evaluations, such as buffers, salts, enzymes, enzyme co-factors, substrates, detection reagents, and the like. Other components, such as buffers and solutions for the isolation and/or treatment of a test sample (e.g., pretreatment reagents), also can be included in the kit. The kit can additionally include one or more other controls. One or more of the components of the kit can be lyophilized, in which case the kit can further comprise reagents suitable for the reconstitution of the lyophilized components.

**[00167]** The kit may also comprise one or more containers, such as vials or bottles, with each container containing a separate reagent. The various components of the kit optionally are provided in suitable containers as necessary, e.g., a microtiter plate. The kit can further include containers for holding or storing a sample (e.g., a container or cartridge for a blood sample). Where appropriate, the kit optionally also can contain reaction vessels, mixing vessels, and other components that facilitate the preparation of reagents or the test sample. The kit can also include one or more instrument for assisting with obtaining a test sample, such as a syringe, pipette, forceps, measured spoon, or the like.

## EXAMPLES

### Example 1

#### Materials and Methods

**[00168] Patients:** In an initial exploratory study, whole blood (40 mL) was obtained from 5 normotensive and 7 hypertensive subjects recruited at Vanderbilt. One normotensive subject was sampled on 2 separate days to obtain a technical replicate that could be used to test the internal consistency of the RNAseq assay. An additional 6 normotensive and 9 hypertensive subjects were recruited for the validation cohort. Hypertension was defined as a systolic

blood pressure greater than 140 mmHg, a diastolic blood pressure greater than 90 mmHg, or treatment with antihypertensive agents, regardless of blood pressure. Exclusion criteria were confirmed or suspected secondary causes of hypertension, diabetes mellitus type I or II, concomitant illness requiring corticosteroids or immunosuppressants, recent (within 3 months) vaccination against any infectious agent, active ongoing malignancy, severe psychiatric disorders, or the presence of HIV/AIDS. Informed consent was obtained prior to the blood draw. The protocol was approved by the Vanderbilt Institutional Review Board and conforms to recognized standards of the US Federal Policy for the Protection of Human Subjects.

**[00169] Monocyte Isolation and RNA extraction:** Whole blood was mixed 1:1 with cold PBS + EDTA. The mixture was layered on top of Ficoll (GE Healthcare Life Sciences, Pittsburgh, PA) and centrifuged for 30 minutes. The 'buffy coat' layer was isolated and washed 3 times with cold PBS + EDTA. The isolated PBMCs were stained using Monocyte Isolation kit II, human (Miltenyi Biotech, Bergisch Gladbach, Germany) and the monocytes were negatively selected using an AutoMACs cell separator. Monocytes were spun down and RNA was extracted using an RNeasy kit (Qiagen, Hilden, Germany), which included a DNaseI treatment step. The purity and quantity of RNA samples were measured using a Denovix DS-11 Spectrophotometer or a NanoDrop ND-1000 Spectrophotometer.

**[00170] RNA Sequencing:** cDNA library construction and RNA sequencing was performed by VANTAGE (Vanderbilt Technologies for Advanced Genomics). cDNA Library preparation was accomplished using the Illumina TruSeq stranded mRNA Sample Preparation Kit, and Rev. D of the protocol. Samples were sequenced on the Illumina HiSeq 2500 using v3 SBS chemistry. Libraries were sequenced on a Single Read 50bp run at 30 million passing filter reads/sample.

**[00171] RNA Sequencing Analysis:** A total of 13 samples were obtained from 12 patients. Based on post-alignment quality assurance and control (QA/QC), all samples were of high fidelity; i.e., Phred quality score =  $37.00 \pm 0.31$ , indicating a high probability that the bases were accurately identified. The Phred score =  $-10 \cdot \log_{10}(\text{Probability of Error})$ . Samples were separated into two groups: hypertensive (n = 7) and normotensive (n = 5). Two samples were collected for one of the 5 normotensive subjects (technical replicates), obtained on separate days, allowing us to perform two separate sets of analyses to increase the robustness of the data and reduce false positives due to RNASeq technical variation. For all 13 samples, the base call accuracy was estimated to be > 99.9%. Libraries were sequenced on a Single Read 50bp run at 30 million passing filter reads/sample. Total reads were 35,021,078 +/- 2.7M, and 86% +/- 0.84% of reads were aligned to the transcriptome.

Statistical analysis for RNAseq was performed using Partek Flow, with the following parameters: Alignment: STAR and TopHat2/Bowtie2; Quantification: Cufflinks and P/E (Li, et al. *Bioinformatics* **2010**, 26, 493-500; Statistics: Cuffdiff, GSA, and ANOVA; Annotations: RefSeq and Aceview; p value adjustment for multiple hypothesis testing: Benjamini & Hochberg). Analysis 1 included all hypertensive and normotensive subjects (true biological replicates), with the normotensive replicated subject represented by the first sample. Analysis 2 was identical to Analysis 1, except the second sample from that subject was used. While we were interested in obtaining a global view of transcriptional differences between hypertensive and normotensive subjects, we especially wanted to identify transcripts with the highest likelihood of being true and reproducible findings. For this purpose, we employed 12 separate methodologies (6 each for Analysis 1 and 2), using various combinations of alignment, quantification, statistical, and annotation strategies.

**[00172] Principal Component Analysis (PCA) and Ingenuity Pathway Analysis (IPA) including upstream regulator analysis:** PCA (with correlation matrix) and hierarchical clustering (with Euclidian distance and Average linkage) were performed using Partek Genomics Suite 6.6. Functional analysis was performed using IPA, Winter Release 2017 (<http://www.ingenuity.com>). Upstream regulator analysis, also performed within IPA, calculates two statistical values for each regulator molecule within Ingenuity's Knowledge base: (1) the overlap p-value, which measures whether there is a statistically significant overlap between the gene list of interest and genes that are regulated by the upstream factor and (2) the Z-score, which infers the likely activation states of upstream regulators. Upstream regulators with positive and negative Z scores of 2 or greater are considered significantly activated or inhibited, respectively.

**[00173] Multivariate regression analyses:** Stepwise multivariate regression analyses were carried out to identify genes, the expression of which ( $\log_{10}$  of normalized RPKM; reads per kilobase per million mapped reads) could be a determinant of blood pressure. Univariate correlation analysis was used for hypothesis generation, i.e. identification of candidate regressor genes. If the expression of a gene correlated with MAP within one group of subjects (either controls or hypertensive patients) or within both, the gene was considered a candidate regressor and included in the multivariate analysis. In contrast, if the expression of a gene only correlated with MAP in all subjects analyzed together, it was not included as a hypothetical regressor. This is because these apparent univariate correlations may simply be driven by the two different levels of blood pressure and gene expression in the two groups of subjects. A p-value <0.05 was considered significant.

**[00174] Quantitative RT-PCR:** Monocyte RNA was converted to cDNA using a High Capacity cDNA Reverse Transcriptase Kit (Applied Biosystems, Foster City, CA). The cDNA was then probed for the following genes (all probes purchased from Taqman [ThermoFisher Scientific, Waltham, MA]): Arg1, CCL4, MMP8, VSIG4, PGLYRP1 and IL18RAP. Results were normalized to GAPDH and subsequently normalized to one of the normotensive patients. The data are plotted as Relative Quantification values.

**[00175] Gene expression correlation in African Americans:** RNA sequencing was performed on whole blood mRNA of self-reported African Americans from the Morehouse School of Medicine subset of the Minority Health Genomics and Translational Research Bio-Repository Database (MH-GRID) as described previously (Gaye, et al. *PloS One* **2017**, *12*, e0187290). For this analysis, total RNA was extracted from whole blood using MagMAX for Stabilized Blood Tubes RNA Isolation Kit (Life Technologies, Carlsbad, CA). TruSeq (Illumina, San Diego, CA) was then used to convert total RNA into cDNA sequencing libraries. cDNA libraries underwent quantitative RT-PCR using the KAPA Library Quant Kit (KAPA Biosystems, Wilmington, MA). Expression levels defined as read counts were determined using a Bowtie2-based pipeline for alignment with read counts determined using RSEM. Expression was normalized using the weighted trimmed mean of M-values (TMM) method. Correlation between the normalized expression of LTF, PGLYRP1, and IL18RAP with MAP or estimated glomerular filtration rate (eGFR) was assessed by linear regression in 76 hypertensive patients. Four models were fitted: (1) without covariates, (2) adjusting for age, (3) adjusting for gender, (4) adjusting for BMI, and (5) adjusting for age, gender, and BMI.

**[00176] Phenome-wide Association Study (PheWAS):** This analysis was performed on a cohort from BioVU, the Vanderbilt DNA databank that links DNA extracted from discarded blood samples to de-identified EHRs. BioVU operated on an opt-out basis until January 2015 and on an opt-in basis since then (Roden et al. *Clin. Pharmacol. Ther.* **2008**, *84*, 362-369). The phenotypic data in BioVU are de-identified and the study was approved by the Vanderbilt Institutional Review Board as "non-human subjects" research. PheWAS results were generated on a cohort of 29,713 self-identified Caucasian/non-Hispanic patients of European ancestry with available HumanCoreExome BeadChip (Illumina; San Diego, CA) genotyping. The mean age of the individuals was 55.4 years and 53% were female. Ancestry was determined using STRUCTURE (Porrás-Hurtado, et al. *Frontiers in Genetics* **2013**, *4*, 98). Case/control status was determined by aggregating ICD-9 billing codes using a phecode map (version 1.2) (Wei et al., *PloS One* **2017**, *12*, e0175508). We required phenotypes to have at least 40 cases to be included in the PheWAS. A total of 1,416

phenotypes met this requirement and were tested for association with the LTF SNP (rs1126478). An association test was performed for each phenotype/genotype pair using an additive model. Logistic regression was performed with age and sex as covariates. The analysis was run using Plink version 1.90 (<https://www.cog-genomics.org/plink2>).

**[00177] Case-control genetic study:** Cases with hypertension and controls without hypertension were identified in BioVU, a de-identified electronic health record (EHR) combined with genetic information as described above (Roden et al. *Clin. Pharmacol. Ther.* **2008**, 84, 362-369). Hypertensive cases and control non-hypertensive individuals were identified using a rigorous, validated random forest model which utilizes age, billing codes, medications, blood pressure readings, pulse, outpatient visits, counts of types of clinical notes, and counts of hypertension-related concepts extracted from clinical notes to identify hypertensive and control individuals in the medical record with a high degree of accuracy (Teixeira et al. *J. Am. Med. Inform. Assoc.* **2017**, 24, 162-171). Cases and controls were restricted to Caucasian adults with age at last encounter less than 80 and greater than 18 years old. Records were excluded with missing data for BMI or age at last encounter, or for BMI less than 16 kg/m<sup>2</sup> or greater than 100 kg/m<sup>2</sup> as these were likely erroneously recorded in the EHR. For each case and control, date of birth, age at last encounter, sex, race, date of death, and median body mass index (BMI) were extracted. Type 2 diabetes was defined using a published algorithm involving medications, laboratory values, and diagnoses (Kho et al. *J. Am. Med. Inform. Assoc.* **2012**, 19, 212-218). Coronary artery disease (CAD) was defined by counting patients who had at least 2 ICD codes of 410.\* (acute myocardial infarction), 411.\* (other acute and subacute forms of ischemic heart disease), 412.\* (old myocardial infarction), 413.\* (angina pectoris), 414.\* (other forms of chronic ischemic heart disease), V45.82 (percutaneous transluminal coronary angioplasty status) or at least 1 CPT code of 33534-33536, 33510-33523 (coronary artery bypass graft), 92980-92982, 92984, 92995, 92996 (intracoronary stent and angioplasty). A missense single nucleotide polymorphism in LTF (rs1126478) resulting in an A->G substitution, with the G allele being the minor allele in European cohorts (Videm, et al. *Hum. Immunol.* **2012**, 73, 554-559), was examined. Genotypic (additive) models were tested by logistic regression with weights of 0 for AA (homozygous major allele), 1 for AG (heterozygous), and 2 for GG (homozygous minor allele) genotypes using XLSTAT (New York, NY). Dominant and recessive genetic models were tested by contingency analysis with Fisher's exact test using GraphPad Prism (La Jolla, CA). Logistic regression was performed under a recessive genetic model in the presence of covariates of age, sex, BMI, and presence of CAD and DM2 using XLSTAT. These studies were approved by the Vanderbilt University Institutional Review Board.

[00178] **Data and Statistical Analysis:** The data and statistical analysis comply with the recommendations on experimental design and analysis in pharmacology (*Curtis et al. British Journal of Pharmacology* **2015**, 172, 3461-3471). The nature of the human monocyte profiling, PheWAS, and genetic case-control studies did not permit randomization or blinding. Data are presented as mean  $\pm$  SEM unless otherwise stated. RT-PCR data between groups were analyzed using Student's t tests or Mann-Whitney tests as appropriate. Categorical variables between groups were analyzed using chi-square tests. Fisher's exact test was used for contingency testing for the LTF SNP case-control analysis. The above tests were performed with GraphPad Prism (GraphPad Software, La Jolla, CA). Univariate and multivariate logistic and linear regression were performed using XLSTAT (New York, NY). A p-value  $<0.05$  was considered significant. A Bonferroni corrected p value is also shown for the PheWAS study.

## Example 2

### RNA sequencing and analysis

[00179] The demographics of the 5 normotensive and 7 hypertensive subjects in the original cohort are shown in **TABLE 1**. Hypertensive patients had higher blood pressures despite treatment and slightly higher (albeit not statistically significant) body mass indices (BMI). The strict combinatorial analytical approach described in the Methods yielded a total of 60 transcripts in the monocytes isolated from these subjects that were identified as significantly differentially expressed after multiple-hypothesis correction (p value  $< 0.05$ ; fold difference  $> 1.5$ ) between normotensive and hypertensive groups (**TABLE 2**). These 60 transcripts along with their fold-difference and p-values are shown in **TABLE 3**. A positive fold-difference indicates the gene is upregulated in hypertensive individuals, and a negative fold-difference indicates the gene is downregulated in hypertensive individuals. Hierarchical clustering (**FIG. 1A**) and Principal Components Analysis (PCA) (**FIG. 1B**) of the 60 most robust genes demonstrated that the combined expression profile differentiated hypertensive from normotensive subjects.

| TABLE 1: Demographics table for original cohort. |                             |                             |
|--------------------------------------------------|-----------------------------|-----------------------------|
|                                                  | Normotensive Controls (n=5) | Hypertensive Patients (n=7) |
| Age (years)                                      | 47.9 $\pm$ 6.8              | 50.4 $\pm$ 2.7              |
| Sex (F/M)                                        | 4/1                         | 7/0                         |

|                          |           |            |
|--------------------------|-----------|------------|
| Race (C/AA)              | 5/0       | 6/1        |
| Duration of HTN (years)  | NA        | 8.9±4.8    |
| Systolic BP (mmHg)       | 112.6±7.2 | 136.7±5.7* |
| Diastolic BP (mmHg)      | 64.8±4.8  | 78.5±5.7   |
| MAP (mmHg)               | 80.7±5.0  | 97.9±5.0*  |
| BMI (kg/m <sup>2</sup> ) | 26.9±3.9  | 33.4±3.7   |
| Antihypertensive Drugs:  |           |            |
| ACEi                     |           | 3          |
| ARB                      |           | 2          |
| ACEi + TZ + CCB          |           | 1          |
| CCB                      |           | 1          |

n = number of subjects in each group, F=female, M=male, C=caucasian, AA=African American, HTN = hypertension, BP = blood pressure, MAP = mean arterial pressure, BMI = body mass index. Data are expressed as mean±SEM. ACEi=angiotensin converting enzyme inhibitors; ARB=angiotensin AT1 receptor blockers; TZ=thiazide diuretics; CCB=dihydropyridine calcium channel blockers. Unpaired t-test and chi-square comparisons were performed between groups. \* p<0.05 compared to normotensive controls.

**TABLE 2: Overview of Statistical Results.**

| Alignment                          | Quant      | Stats    | Annot   | Analysis Set 1                            | Analysis Set 2 | Total (1 OR 2) | Common (1 AND 2) |
|------------------------------------|------------|----------|---------|-------------------------------------------|----------------|----------------|------------------|
|                                    |            |          |         | Number RNA entities with p<0.05, FD > 1.5 |                |                |                  |
| STAR                               | Partek E/M | GSA      | RefSeq  | 624                                       | 651            | 810            | 465              |
|                                    |            |          | Aceview | 1,790                                     | 1,670          | 2,280          | 1,180            |
|                                    |            | ANOVA    | RefSeq  | 525                                       | 549            | 698            | 376              |
|                                    |            |          | Aceview | 1,643                                     | 1,535          | 2,104          | 1,074            |
| Bowtie2 + TopHat2                  | Cufflinks  | CuffDiff | RefSeq  | 1,155                                     | 1,115          | 1,659          | 611              |
|                                    |            |          | Aceview | 962                                       | 944            | 1,316          | 590              |
| All genes identified using STAR    |            |          |         | 2,051                                     | 1,956          | 2,620          | 1,387            |
| All genes identified using TopHat2 |            |          |         | 1,763                                     | 1,717          | 2,569          | 911              |

|                                                         |       |       |       |       |
|---------------------------------------------------------|-------|-------|-------|-------|
| <b>All differential genes</b>                           | 3,457 | 3,332 | 4,757 | 2,032 |
| <b>Genes commonly altered in every STAR analysis</b>    | 289   | 290   | 376   | 204   |
| <b>Genes commonly altered in every TopHat2 analysis</b> | 333   | 342   | 381   | 294   |
| <b>Final Stringent Gene List</b>                        | 88    | 80    | 108   | 60    |

Analysis Sets 1 and 2 are defined in more detail in the Methods section.  
 Quant = Quantification, Stats = Statistics, Annot = Annotation

| <b>TABLE 3: List of the 60 Significant Genes and their fold-change.</b> |                                                                                                 |                       |           |
|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------|-----------|
| <b>Symbol</b>                                                           | <b>Gene Name</b>                                                                                | <b>p value</b>        | <b>FD</b> |
| ABCA13                                                                  | ATP-binding cassette, sub-family A (ABC1), member 13                                            | $7.0 \times 10^{-03}$ | 48.2      |
| SLPI                                                                    | secretory leukocyte peptidase inhibitor                                                         | $1.0 \times 10^{-02}$ | 18.1      |
| TCN1                                                                    | transcobalamin I (vitamin B12 binding protein, R binder family)                                 | $7.2 \times 10^{-03}$ | 12.7      |
| DEFA4                                                                   | defensin, alpha 4, corticostatin                                                                | $1.7 \times 10^{-02}$ | 11.3      |
| CEACAM8                                                                 | carcinoembryonic antigen-related cell adhesion molecule 8                                       | $8.8 \times 10^{-03}$ | 11.2      |
| CEACAM6                                                                 | carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen) | $1.2 \times 10^{-02}$ | 10.9      |
| CHI3L1                                                                  | chitinase 3-like 1 (cartilage glycoprotein-39)                                                  | $1.2 \times 10^{-02}$ | 10.5      |
| LCN2                                                                    | lipocalin 2                                                                                     | $8.2 \times 10^{-03}$ | 10.1      |
| MMP8                                                                    | matrix metalloproteinase 8 (neutrophil collagenase)                                             | $4.1 \times 10^{-03}$ | 10.0      |
| CCL4                                                                    | chemokine (C-C motif) ligand 4                                                                  | $8.4 \times 10^{-03}$ | 9.6       |
| ATP2C2                                                                  | ATPase, Ca <sup>++</sup> transporting, type 2C, member 2                                        | $1.2 \times 10^{-02}$ | 9.3       |
| MKI67                                                                   | marker of proliferation Ki-67                                                                   | $1.2 \times 10^{-02}$ | 9.0       |
| ARG1                                                                    | arginase 1                                                                                      | $8.6 \times 10^{-03}$ | 8.7       |
| LTF                                                                     | lactotransferrin                                                                                | $5.0 \times 10^{-03}$ | 8.6       |
| HJURP                                                                   | Holliday junction recognition protein                                                           | $1.1 \times 10^{-02}$ | 8.4       |
| CEACAM1                                                                 | carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)                | $1.4 \times 10^{-02}$ | 8.3       |

|          |                                                                                        |                       |     |
|----------|----------------------------------------------------------------------------------------|-----------------------|-----|
| PGLYRP1  | peptidoglycan recognition protein 1                                                    | $6.1 \times 10^{-03}$ | 8.2 |
| RPL9     | ribosomal protein L9                                                                   | $1.3 \times 10^{-03}$ | 8.2 |
| CAMP     | cathelicidin antimicrobial peptide                                                     | $3.7 \times 10^{-03}$ | 7.5 |
| RORA     | RAR-related orphan receptor A                                                          | $1.1 \times 10^{-02}$ | 7.5 |
| CRISP3   | cysteine-rich secretory protein 3                                                      | $7.4 \times 10^{-03}$ | 6.6 |
| FAM20A   | family with sequence similarity 20, member A                                           | $2.7 \times 10^{-03}$ | 6.3 |
| PDZD4    | PDZ domain containing 4                                                                | $1.9 \times 10^{-03}$ | 6.0 |
| SAMD3    | sterile alpha motif domain containing 3                                                | $2.4 \times 10^{-03}$ | 5.9 |
| IL18RAP  | interleukin 18 receptor accessory protein                                              | $6.5 \times 10^{-03}$ | 5.7 |
| SH2D1A   | SH2 domain containing 1A                                                               | $8.4 \times 10^{-03}$ | 5.5 |
| PTGDR    | prostaglandin D2 receptor (DP)                                                         | $3.4 \times 10^{-03}$ | 5.4 |
| CD247    | CD247 molecule                                                                         | $1.4 \times 10^{-02}$ | 5.4 |
| GZMH     | granzyme H (cathepsin G-like 2, protein h-CCPX)                                        | $3.7 \times 10^{-02}$ | 5.3 |
| PTGES    | prostaglandin E synthase                                                               | $1.3 \times 10^{-02}$ | 4.8 |
| AFAP1    | actin filament associated protein 1                                                    | $1.6 \times 10^{-03}$ | 4.6 |
| OLR1     | oxidized low density lipoprotein (lectin-like) receptor 1                              | $1.7 \times 10^{-02}$ | 4.4 |
| HS3ST3B1 | heparan sulfate (glucosamine) 3-O-sulfotransferase 3B1                                 | $7.9 \times 10^{-03}$ | 4.3 |
| NKG7     | natural killer cell granule protein 7                                                  | $1.6 \times 10^{-02}$ | 4.1 |
| MMP9     | matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase) | $6.8 \times 10^{-03}$ | 4.1 |
| CCL3     | chemokine (C-C motif) ligand 3                                                         | $8.8 \times 10^{-03}$ | 4.0 |
| RASGRP1  | RAS guanyl releasing protein 1 (calcium and DAG-regulated)                             | $5.5 \times 10^{-03}$ | 3.8 |
| TNF      | tumor necrosis factor                                                                  | $3.2 \times 10^{-03}$ | 3.1 |
| ANKRD33B | ankyrin repeat domain 33B                                                              | $1.5 \times 10^{-03}$ | 2.4 |
| NFKBIZ   | nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta     | $6.0 \times 10^{-03}$ | 2.3 |
| MMRN1    | multimerin 1                                                                           | $1.6 \times 10^{-02}$ | 2.3 |

|           |                                                                                     |                       |      |
|-----------|-------------------------------------------------------------------------------------|-----------------------|------|
| CXCR1     | chemokine (C-X-C motif) receptor 1                                                  | $1.9 \times 10^{-02}$ | 2.3  |
| NFKBIA    | nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha | $2.7 \times 10^{-03}$ | 2.2  |
| CPNE5     | copine V                                                                            | $1.6 \times 10^{-02}$ | 2.0  |
| CETP      | cholesteryl ester transfer protein, plasma                                          | $2.5 \times 10^{-02}$ | 2.0  |
| FCHO2     | FCH domain only 2                                                                   | $1.2 \times 10^{-04}$ | 1.9  |
| MS4A4A    | membrane-spanning 4-domains, subfamily A, member 4A                                 | $2.5 \times 10^{-03}$ | 1.8  |
| MCTP2     | multiple C2 domains, transmembrane 2                                                | $1.0 \times 10^{-03}$ | 1.8  |
| JAK3      | Janus kinase 3                                                                      | $1.0 \times 10^{-03}$ | 1.7  |
| B4GALT5   | UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 5                   | $9.8 \times 10^{-03}$ | 1.6  |
| GPRIN3    | GPRIN family member 3                                                               | $9.0 \times 10^{-03}$ | 1.6  |
| FHL1      | four and a half LIM domains 1                                                       | $5.5 \times 10^{-03}$ | 1.6  |
| CR1       | complement component (3b/4b) receptor 1 (Knops blood group)                         | $2.2 \times 10^{-02}$ | 1.5  |
| FCER1A    | Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide                | $1.3 \times 10^{-02}$ | -1.6 |
| PID1      | phosphotyrosine interaction domain containing 1                                     | $9.9 \times 10^{-03}$ | -1.6 |
| ALDH1A1   | aldehyde dehydrogenase 1 family, member A1                                          | $3.0 \times 10^{-03}$ | -1.6 |
| FLT3      | fms-related tyrosine kinase 3                                                       | $1.6 \times 10^{-02}$ | -1.7 |
| TNFRSF12A | tumor necrosis factor receptor superfamily, member 12A                              | $2.0 \times 10^{-02}$ | -1.8 |
| VSIG4     | V-set and immunoglobulin domain containing 4                                        | $5.4 \times 10^{-03}$ | -1.9 |
| ACCS      | 1-aminocyclopropane-1-carboxylate synthase homolog (Arabidopsis)(non-functional)    | $4.0 \times 10^{-03}$ | -2.1 |

P value = average p value across 12 analyses, including Cuffdiff with multiple hypothesis correction

FD = average fold- difference across all 12 analyses, after conversion of Cuffdiff log2 values to fold-difference values. A positive fold-difference indicates the gene is upregulated in hypertensive individuals and a negative fold-difference indicates the gene is downregulated in hypertensive individuals.

**[00180]** Using known relationships between gene expression changes and upstream factors involved in their regulation, upstream regulatory analysis using Ingenuity Pathway

Analysis (IPA) inferred activation of IL-1 $\beta$ , nuclear factor kappa B (NF- $\kappa$ B), and the adaptor protein myeloid differentiation primary response 88 (MYD88) based on the differential gene expression in hypertensive monocytes. Interestingly, these three molecules are part of the IL-1 $\beta$  signaling pathway. Indeed, 21 of the 60 differentially expressed genes identified by RNASeq are related to IL-1 $\beta$  (FIG. 1C). We also employed IPA to identify non-biased and significantly enriched functions in these 60 genes. The most statistically enriched disorder was "Inflammatory Response", with a  $p$  value range of  $5.4 \times 10^{-4}$  to  $4.6 \times 10^{-15}$  (TABLE 4), which essentially indicates a very low probability that this functional category would be represented by a significant portion of 60 randomly selected genes. Based on causal prediction analysis, which uses individual relationships curated from the literature to infer functional directionality from transcriptional directionality (i.e., up- or down-regulation of each functionally related gene), the functions associated with inflammatory responses were activated (Z score= 2.595 to 2.943). Enriched molecular and cellular functions include immune cell migration and signaling, phagocytosis, proliferation of vascular smooth muscle cells, and T cell development (TABLE 4).

| TABLE 4: Functional Analysis of Significant Genes. |                                            |     |                      |           |
|----------------------------------------------------|--------------------------------------------|-----|----------------------|-----------|
| Top Diseases and Bio Functions                     | Enrichment                                 |     | Predicted Activation |           |
|                                                    | p value                                    | No. | *Z score             | Direction |
| DISEASES AND DISORDERS                             |                                            |     |                      |           |
| <b>Inflammatory Response</b>                       | $5.4 \times 10^{-4} - 4.6 \times 10^{-15}$ | 33  | NA                   |           |
| <i>Activation of leukocytes</i>                    | $4.6 \times 10^{-15}$                      | 22  | 2.943                | Activated |
| <i>Inflammatory response</i>                       | $4.2 \times 10^{-13}$                      | 21  | 2.670                | Activated |
| <i>Activation of myeloid cells</i>                 | $7.5 \times 10^{-13}$                      | 15  | 2.685                | Activated |
| <i>Activation of phagocytes</i>                    | $2.5 \times 10^{-12}$                      | 15  | 2.569                | Activated |
| <i>Activation of macrophages</i>                   | $2.0 \times 10^{-11}$                      | 12  | 2.595                | Activated |
| MOLECULAR AND CELLULAR FUNCTIONS                   |                                            |     |                      |           |
| <b>Cellular Movement</b>                           | $5.8 \times 10^{-4} - 4.4 \times 10^{-16}$ | 32  | NA                   |           |
| <i>Cell movement of mononuclear leukocytes</i>     | $6.5 \times 10^{-12}$                      | 16  | 2.975                | Activated |
| <i>Cell movement of lymphocytes</i>                | $9.7 \times 10^{-11}$                      | 14  | 2.802                | Activated |
| <i>Migration of cells</i>                          | $1.0 \times 10^{-10}$                      | 28  | 2.668                | Activated |

|                                                      |                                            |    |       |           |
|------------------------------------------------------|--------------------------------------------|----|-------|-----------|
| <i>Cell movement of monocytes</i>                    | $5.9 \times 10^{-8}$                       | 8  | 2.740 | Activated |
| <i>Migration of mononuclear leukocytes</i>           | $7.0 \times 10^{-8}$                       | 11 | 2.823 | Activated |
| <b>Cell-cell Signaling and Interaction</b>           | $5.5 \times 10^{-4} - 4.6 \times 10^{-16}$ | 30 | NA    |           |
| <b>Cellular Function and Maintenance</b>             | $5.5 \times 10^{-4} - 4.0 \times 10^{-10}$ | 28 | NA    |           |
| <i>Engulfment of cells</i>                           | $1.7 \times 10^{-6}$                       | 10 | 2.649 | Activated |
| <i>Phagocytosis of cells</i>                         | $3.7 \times 10^{-5}$                       | 7  | 2.050 | Activated |
| Cellular Development                                 | $5.7 \times 10^{-4} - 1.5 \times 10^{-9}$  | 29 |       |           |
| <i>Proliferation of smooth muscle cells</i>          | $5.7 \times 10^{-5}$                       | 7  | 2.006 | Activated |
| <i>Proliferation of vascular smooth muscle cells</i> | $1.4 \times 10^{-4}$                       | 5  | 2.173 | Activated |
| <i>Development of lymphocytes</i>                    | $2.2 \times 10^{-4}$                       | 9  | 2.264 | Activated |
| <i>T cell development</i>                            | $5.5 \times 10^{-4}$                       | 8  | 2.609 | Activated |
| <b>PHYSIOLOGICAL SYSTEM DEVELOPMENT AND FUNCTION</b> |                                            |    |       |           |
| <b>Immune Cell Trafficking</b>                       | $5.6 \times 10^{-4} - 4.4 \times 10^{-16}$ | 30 | NA    |           |
| <b>Hematological Dev/Function</b>                    | $5.8 \times 10^{-4} - 2.7 \times 10^{-15}$ | 31 | NA    |           |
| <b>Tissue Morphology</b>                             | $5.8 \times 10^{-4} - 8.4 \times 10^{-10}$ | 27 | NA    |           |
| <i>Quantity of CD4+ T-lymphocytes</i>                | $1.2 \times 10^{-5}$                       | 6  | 2.200 | Activated |

Main functional categories shown in bold, Sub-categories are italicized. \*Positive and negative Z scores of >2.0 are generally considered as significant for activation and inhibition, respectively. Functional categories are arranged in a "tree format", similar to the Gene Ontology (GO) Consortium database. A range of p values is thus provided for upper branches that encompass multiple sub-categories (each of which includes its own p value calculation).

### Example 3

#### Regression Analysis of Gene Determinants of Blood Pressure

[00181] To narrow the list of 60 differentially expressed genes, we performed univariate and multivariate regression analyses in controls, hypertensive individuals, and/or all subjects together to identify transcripts that significantly correlated with mean arterial pressure (MAP).

The expression of 23 genes ( $\log_{10}$  normalized RPKM [reads per kilobase per million mapped reads]) correlated significantly with MAP in univariate analyses in normotensive controls, hypertensive individuals, or in these groups and all subjects together. However, by multivariate analyses, only lactoferrin (LTF) and peptidoglycan recognition protein 1 (PGLYRP1) remained significantly correlated with MAP in normotensive controls, and granzyme H (GZMH) remained significantly correlated with MAP in hypertensive subjects. Interestingly, the expression of interleukin-18 receptor accessory protein (IL18RAP) correlated significantly with MAP of controls ( $r=0.93$ ), hypertensive patients ( $r=0.78$ ) and all subjects analyzed together ( $r=0.89$ ). In summary, the expression of four genes, LTF, PGLYRP1, GZMH, and IL18RAP were significantly correlated with MAP in normotensive and/or hypertensive subjects by multivariate analysis. The univariate correlations of these genes with MAP are shown in **FIG. 2**. The corresponding multivariate models for MAP based on expression of these genes are shown in **TABLE 5**.

**TABLE 5: Multivariate Regression Models for MAP using expression levels of LTF, PGLYRP1, GZMH, and/or IL18RAP.**

| Gene            | Group | Model                                                                                                         | R <sup>2</sup> | p-value |
|-----------------|-------|---------------------------------------------------------------------------------------------------------------|----------------|---------|
| LTF and PGLYRP1 | C     | MAP = 60.01 ( $\pm 0.41$ ) + 14.60 ( $\pm 0.53$ )* $\log_{10}$ LTF + 4.54 ( $\pm 0.59$ )* $\log_{10}$ PGLYRP1 | 0.99           | p<0.01  |
| GZMH            | H     | MAP = 98.45 ( $\pm 2.60$ ) + 24.28 ( $\pm 5.86$ )* $\log_{10}$ GZMH                                           | 0.77           | p<0.01  |
| IL18RAP         | All   | MAP = 99.15 ( $\pm 2.50$ ) + 26.75 ( $\pm 4.42$ )* $\log_{10}$ IL18RAP                                        | 0.79           | p<0.01  |

C = normotensive controls, H = hypertensive patients, All = all subjects analyzed together

#### Example 4

##### Quantitative RT-PCR in a validation cohort

**[00182]** To determine the robustness of our observed gene expression changes in peripheral monocytes, we recruited a separate validation cohort of 6 normotensive and 9 hypertensive subjects. As shown in **TABLE 6**, age, blood pressures, and BMI were slightly but not significantly higher in hypertensive individuals compared to normotensives in this cohort. Frequency and type of antihypertensive treatment also varied slightly from the original cohort. As in the prior cohort, the majority of the patients were Caucasian. We isolated peripheral blood monocytes and examined the expression of the 4 genes that were found to significantly correlate with MAP (LTF, GZMH, IL18RAP, and PGLYRP1) by quantitative RT-PCR. All but GZMH remained significantly elevated in peripheral monocytes

of hypertensive individuals relative to controls (with GZMH showing a trend but not reaching statistical significance) (FIG. 2). As further validation for the original observed gene expression changes, we investigated the expression of 4 additional genes with known or predicted effects on inflammation (ARG1, CCL4, MMP8, and VSIG4). Expression of ARG1, VSIG4, and MMP8 was significantly altered in the predicted direction in hypertensive individuals in the validation cohort (FIG. 6), demonstrating the robustness and reproducibility of the gene expression changes observed in the original cohort.

| TABLE 6: Demographics Table for Validation Cohort. |                             |                             |
|----------------------------------------------------|-----------------------------|-----------------------------|
|                                                    | Normotensive Controls (n=6) | Hypertensive Patients (n=9) |
| Age (years)                                        | 42.2±6.3                    | 50.4±3.2                    |
| Sex (F/M)                                          | 3/3                         | 7/2                         |
| Race (C/AA/A)                                      | 4/1/1                       | 7/2/0                       |
| Duration of HTN (years)                            | NA                          | 15.0±3.8                    |
| Systolic BP (mmHg)                                 | 128.0±5.5                   | 140.4±8.9                   |
| Diastolic BP (mmHg)                                | 72.7±3.0                    | 78.3±2.5                    |
| MAP (mmHg)                                         | 91.1±3.1                    | 99.0±4.3                    |
| BMI (kg/m <sup>2</sup> )                           | 25.7±2.6                    | 30.2±2.4                    |
| Antihypertensive Drugs:                            |                             |                             |
| None                                               |                             | 1                           |
| TZ + TMT                                           |                             | 2                           |
| CCB + α1B                                          |                             | 1                           |
| CCB + SP                                           |                             | 1                           |
| ACEi                                               |                             | 2                           |
| ACEi + TZ                                          |                             | 1                           |
| ARB + TZ + CCB                                     |                             | 1                           |

n = number of subjects in each group, F=female, M=male, C=caucasian, AA=African American, A=Asian, HTN = hypertension, BP = blood pressure, MAP = mean arterial pressure, BMI = body mass index. Data are expressed as mean±SEM. TZ=thiazide diuretics; TMT=triamterene; CCB=dihydropyridine calcium channel blockers; α1B=peripheral alpha-1 adrenergic receptor blockers; SP=spironolactone; ACEi=angiotensin converting enzyme inhibitors; ARB=angiotensin AT1 receptor blockers. Unpaired t-test and chi-square

comparisons were performed between groups. No measures met significance threshold compared to normotensive controls of  $p < 0.05$ .

### Example 5

#### Correlation between inflammasome genes and MAP

**[00183]** It was examined whether a correlation exists between inflammasome genes and Mean Arterial Pressure (MAP), using RNA-seq data from the MH-GRID. The expression data was from whole blood messenger RNA (mRNA) sequencing data of 177 self-reported African American from the Morehouse School of Medicine subset of the MH-GRID. Total RNA extraction was carried out using MagMAX<sup>TM</sup> for Stabilized Blood Tubes RNA Isolation Kit as recommended by vendor (Life Technologies, Carlsbad, CA). For library preparation, total RNA samples were converted into indexed cDNA sequencing libraries using Illumina's TruSeq sample kits (Stranded Total RNA). After PCR amplification, the final libraries were quantitated by qPCR (KAPA Library Quant Kit, KAPA Biosystems). Expression quantification was carried out using a pipeline based on BowTie2 as alignment tool and the read count were determined using RSEM. The expression was normalized using the weighted trimmed mean of M-values (TMM) method.

**[00184]** The correlation between the normalized expression of 7 genes (LTF, GZMH, PGLYRP1, IL18RAP, ARG1, VSIG4, and IL1B) and Mean Arterial Pressure (MAP) was assessed by linear regression in all the samples ( $n=177$ ), hypertensives ( $n=76$ ) subset, and normotensives subset ( $n=101$ ). Four models were fitted: (1) without covariates, (2) adjusting for age, (3) adjusting for BMI, and (4) adjusting for age and BMI.

**[00185]** For the linear regression the outcome, MAP was not standardized, hence the difference of the estimate between the beta coefficient and the Pearson correlation value reported in the correlation plot; the two values would be the same if regression was conducted with a standardized MAP.

**[00186]** It was found that PGLYRP1 is significantly correlated with MAP across all models, except for the one adjusted for age, in the whole samples set (hypertensives and normotensives).

**[00187]** It was found that IL18RAP is significantly correlated with MAP, across all 4 models, in the hypertensives subset of samples.

**[00188]** It was found that IL1B is significantly correlated with MAP, across all 4 models, in the whole sample set and in the hypertensive subset.

**[00189] Correlation with MAP across all the samples (N = 177):** It was found that IL1B is significantly correlated with MAP across all 4 models, and PGLYRP1 is significantly correlated with MAP except in the model adjusted for age.

**[00190] Correlation with MAP across Hypertensives (N = 76):** It was found that IL18RAP is significantly correlated with MAP in all 4 models and IL1B is correlated with MAP in the adjusted models.

**[00191] Correlation with MAP across Normotensives (N = 101):** It was found that none of the 6 genes is correlated with MAP in any of the models.

### Example 6

#### **Correlation of Mean Arterial Pressure (MAP) and/or Glomerular Filtration Rate (GFR) with the expression of IL18RAP and PGLYRP1**

**[00192]** It was examined whether Mean Arterial Pressure (MAP) and/or Glomerular Filtration Rate (GFR) is correlated with the expression of IL18RAP and PGLYRP1. The expression data were from whole blood messenger RNA (mRNA) sequencing data of 76 self-reported African American from the Morehouse School of Medicine subset of the Minority Health Genomics and Translational Research Bio-Repository Database (MH-GRID). Total RNA extraction was carried out using MagMAX™ for Stabilized Blood Tubes RNA Isolation Kit as recommended by vendor (Life Technologies, Carlsbad, CA). For library preparation, total RNA samples were converted into indexed cDNA sequencing libraries using Illumina's TruSeq sample kits (Stranded Total RNA). After PCR amplification, the final libraries were quantitated by qPCR (KAPA Library Quant Kit, KAPA Biosystems). Expression quantification was carried out using a pipeline based on BowTie2 as alignment tool and the read count were determined using RSEM.

**[00193]** For this analysis, the expression of the genes (i.e. read counts) was normalized using the weighted trimmed mean of M-values (TMM) method. The distribution of the two clinical variables, mean arterial pressure (MAP) and estimated glomerular filtration rate (eGFR), across the 76 hypertensives subjects, are shown graphically in FIG. 7.

**[00194] MAP and Gfr and Il18rap Gene Expression:** A two-sided Pearson correlation test was conducted between MAP and IL18RAP expression and between eGFR and IL18RAP expression. The results of the two tests are summarized in FIG. 7, which show a statistically significant correlation between IL18RAP expression and both MAP ( $r=0.274$ ,  $p=0.017$ , 95% CI=[0.052,0.471]) and eGFR ( $r=-0.227$ ,  $p=0.048$ , 95% CI=[-0.431,-0.002]).

**[00195] MAP and Gfr and Pglyrp1 Gene Expression:** A two-sided Pearson correlation test was conducted between MAP and PGLYRP1 expression eGFR and PGLYRP1 expression. The results of the 2 tests summarized are in **FIG. 8** show a statistically significant negative correlation ( $r=-0.242$ ,  $p=0.035$ , 95% CI= $[-0.443,-0.018]$ ) between PGLYRP1 expression and eGFR levels and a statistically non-significant negative correlation between MAP and PGLYRP1 ( $r=-0.121$ ,  $p=0.299$ , 95% CI= $[-0.337,0.108]$ ).

### Example 7

#### Correlation between gene expression and MAP in African Americans

**[00196]** We then elected to test the three differentially expressed genes in the original and validation cohorts that associated with MAP (LTF, PGLYRP1, and IL18RAP) in a larger independent cohort from the Minority Health Genomics and Translational Research Bio-Repository Database (MH-GRID) (Gaye, et al. *PLoS One* 2017, 12, e0187290). This cohort importantly differs from our original and validation cohorts by being composed exclusively of hypertensive African Americans. Also, gene expression was determined by RNA sequencing of whole blood rather than peripheral monocytes. Demographics of this cohort are shown in **TABLE 7**. We performed Pearson correlation analysis of mRNA transcript levels of LTF, PGLYRP1, and IL18RAP versus MAP. Interestingly, IL18RAP (but not LTF or PGLYRP1) significantly correlated with MAP in these individuals (**FIG. 4A**), and this correlation remained significant after adjustment for age, gender, and BMI (**TABLE 8**). To determine whether IL18RAP expression may be associated with end-organ damage from HTN, the relationship between IL18RAP expression and estimated glomerular filtration rate (eGFR) was examined in these hypertensive individuals and found to exhibit a significant negative correlation (**FIG. 4B**). This correlation remained significant after adjustment for age, gender, and BMI (**TABLE 8**).

| TABLE 7: Demographics of hypertensive individuals from MH-GRID. |                              |
|-----------------------------------------------------------------|------------------------------|
|                                                                 | Hypertensive Patients (n=76) |
| MAP (mmHg)                                                      | 94±12                        |
| Sex (F/M)                                                       | 37/39                        |
| Age (years)                                                     | 47±6                         |
| BMI                                                             | 35±8                         |
| Antihypertensive Drugs:                                         |                              |

|                           |    |
|---------------------------|----|
| TZ                        | 2  |
| TZ + TMT                  | 3  |
| ACEi + TZ                 | 19 |
| ACEi + LD                 | 1  |
| ARB + TZ                  | 1  |
| ARB + CCB                 | 1  |
| CCB + TZ                  | 10 |
| CCB + SP                  | 1  |
| BB + TZ                   | 5  |
| BB + LD                   | 1  |
| HYD + LD                  | 1  |
| ACEi + TZ + TMT           | 4  |
| ACEi + CCB + TZ           | 8  |
| ARB + CCB + TZ            | 3  |
| CCB + TZ + TMT            | 1  |
| BB + TZ + TMT             | 1  |
| BB + TZ + LD              | 1  |
| BB + ACEi + TZ            | 1  |
| BB + CCB + TZ             | 2  |
| ACEi + CCB + BB + TZ      | 5  |
| ACEi + CCB + BB + LD      | 4  |
| ACEi + BB + TZ + SP + HYD | 1  |

n = number of subjects, MAP=mean arterial pressure, F=female, M=male, BMI=body mass index. Data are expressed as mean±SEM. TZ=thiazide diuretics; TMT=triamterene; ACEi=angiotensin converting enzyme inhibitors; LD=loop diuretics; ARB=angiotensin AT1 receptor blockers; CCB=dihydropyridine calcium channel blockers; SP=spironolactone; BB=beta-blockers; HYD=hydralazine.

**TABLE 8: Linear Regression of IL18RAP expression versus MAP or eGFR with and without adjustment for age, gender and BMI.**

|  | MAP | eGFR |
|--|-----|------|
|--|-----|------|

|                                 | Beta | Std Error | P value | Beta  | Std Error | P value |
|---------------------------------|------|-----------|---------|-------|-----------|---------|
| <b>Gene</b>                     | 0.13 | 0.05      | 0.017   | -0.2  | 0.1       | 0.048   |
| <b>Gene+Age</b>                 | 0.13 | 0.05      | 0.016   | -0.2  | 0.1       | 0.047   |
| <b>Gene+Gender</b>              | 0.12 | 0.05      | 0.024   | -0.24 | 0.1       | 0.017   |
| <b>Gene+BMI</b>                 | 0.13 | 0.05      | 0.013   | -0.21 | 0.1       | 0.047   |
| <b>Gene+Age+<br/>Gender+BMI</b> | 0.12 | 0.05      | 0.024   | -0.24 | 0.1       | 0.02    |

Std error=standard error

### Example 8

#### PheWAS Analysis

**[00197]** We sought to determine whether polymorphisms in the candidate genes are associated with hypertension in a large cohort using BioVU, the Vanderbilt DNA databank that links DNA from discarded blood samples to de-identified electronic health records (PMID 18500243). We identified a single nucleotide polymorphism (SNP) in LTF designated rs1126478 that has been associated with increased levels of LTF in humans. We hypothesized that this SNP would be associated with hypertension in BioVU.

**[00198] Study Populations:** BioVU accrues DNA samples extracted from blood drawn for routine clinical testing. A full description of this resource and its associated ethical, privacy and other protections has been previously published (PMID 18500243). At the time of this study, BioVU contained approximately 210,000 patients with DNA and 28,839 self-identified white/non-Hispanic patients with available Illumina HumanCoreExome BeadChip (San Diego, CA) genotyping were included. The mean age of the individuals was 55.4 years and 53% were female. BioVU operated on an opt-out basis until January 2015 and on an opt-in basis since (PMID 18500243). The phenotypic data in BioVU are all de-identified and the study was designated "non-human subjects" research by the Vanderbilt Institutional Review Board.

**[00199]** The PheWAS results were generated on a cohort of 29,713 individuals of European ancestry genotyped on the Exome BeadChip and linked to EHR data. Ancestry was determined using STRUCTURE (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3665925/>). Case/control status was determined by aggregating ICD-9 billing codes using a phecode map (version 1.2,

<https://www.phewascatalog.org/phcodes>, Wei, et al., *PLoS One* **2017**, 12, e0175508). We required phenotypes to have at least 40 cases to be included in the PheWAS; a total of 1,418 phenotypes were tested for each SNP. An association test was performed for each phenotype/genotype pair using logistic regression with age and sex as covariates. The analysis was run using Plink version 1.90 (<https://www.cog-genomics.org/plink2>). Results are shown in **FIG. 9**.

**[00200]** Although not significant following Bonferonni correction, the top cardiovascular disorder codes associated with the rs1126478 SNP in LTF was hypertension (OR=1.069, P=0.0018) and essential hypertension (OR=1.067, P= 0.0027). This finding is strongly suggestive of a link between LTF levels and hypertension.

### Example 9

#### Phenome-wide association of an LTF SNP

**[00201]** To further evaluate the role of the differentially expressed genes in our original and validation cohorts that correlate with MAP (LTF, IL18RAP, and PGLYRP1), we sought to identify missense SNPs that alter protein function in these genes. Prior reports demonstrated a missense SNP (A -> G) in LTF (rs1126478) that changes a lysine to arginine at position 47. The G allele (arginine) is the minor allele in European cohorts and increases LTF protein levels while decreasing its antimicrobial protein function. We were unable to identify missense SNPs altering protein function for PGLYRP1 or IL18RAP in the literature.

**[00202]** Using a European cohort within BioVU, a de-identified electronic medical record coupled with genetic information at Vanderbilt University Medical Center, we performed a phenome-wide association study (PheWAS) on the missense LTF SNP rs1126478 (Denny et al. *Bioinformatics* **2010**, 26, 1205-1210). In our PheWAS analysis, 'Hypertension' and 'Essential Hypertension' are separate but clinically similar phecodes. Results revealed that both Hypertension (OR=1.069, p=0.0018) and Essential Hypertension (OR=1.067, p=0.0027) phecodes were among the top 5 phenotypes associated with the minor G allele in an additive model with a p value < 0.05 (**FIG. 5**). Of note, there were no phenotypes significantly associated with the LTF SNP when using a conservative Bonferroni-corrected p value of  $3.5 \times 10^{-5}$ .

### Example 10

#### Hypertension Case-control study of the LTF SNP

**[00203]** Given the significant upregulation of LTF in monocytes of hypertensive individuals, and the over-representation of hypertension phenotypes with a missense SNP in LTF that increases protein levels, we performed a complementary case-control analysis of this SNP in hypertensive and normotensive control patients using a European cohort within BioVU. In contrast to the PheWAS study where disease phenotypes were defined by International Classification of Diseases 9 (ICD-9) codes, this case-control approach permits focused determination of the relationship of the LTF SNP to hypertension using a much more rigorous algorithm for accurate identification of hypertensive individuals from the medical record that incorporates ICD codes, vitals, medications, and natural language processing (Teixeira, et al. *J. Am. Med. Inform. Assoc.* **2017**, 24, 162-171). Using this algorithm, we identified 10,549 hypertensive individuals and 5,038 controls. The hypertensive patients were older with male sex predominance, higher BMI, and increased prevalence of coronary artery disease (CAD) and diabetes mellitus type 2 (DM2), consistent with known risk factors and comorbidities for HTN (**TABLE 9**). We found, using a recessive genetic model, that hypertensive individuals had a significantly increased frequency of homozygosity for the minor allele (GG) of the missense LTF SNP rs1126478 compared to controls (odds ratio 1.16,  $p=0.005$ ) (**TABLE 11**). There was a trend for significance using an additive genetic model (OR 1.05;  $p$  value 0.08) and no significant association of rs1126478 with hypertension using a dominant (OR 1.02;  $p$  value 0.53) genetic model.

| <b>TABLE 9: Demographics of case and control individuals in BioVU.</b> |                                           |                                            |
|------------------------------------------------------------------------|-------------------------------------------|--------------------------------------------|
|                                                                        | <b>Normotensive Controls<br/>(n=5038)</b> | <b>Hypertensive Patients<br/>(n=10549)</b> |
| <b>Female (%)</b>                                                      | 3206 (64)                                 | 5193 (49)**                                |
| <b>Age at last visit (years)</b>                                       | 48±0.2                                    | 63±0.1*                                    |
| <b>BMI (kg/m<sup>2</sup>)</b>                                          | 25.9±0.1                                  | 29.7±0.1*                                  |
| <b>CAD (%)</b>                                                         | 217 (4)                                   | 2909 (28)**                                |
| <b>DM2 (%)</b>                                                         | 114 (2)                                   | 2157 (20)**                                |

BMI=body mass index; CAD=coronary artery disease; DM2=Diabetes mellitus type 2. Age at last visit and BMI represent mean±SEM. \* $p<0.0001$  by Mann-Whitney test compared to normotensive controls. \*\* $p<0.0001$  by Fisher's exact test compared to normotensive controls.

| <b>TABLE 11: Case-control analysis using recessive genetic model for rs1126478.</b> |                              |                              |
|-------------------------------------------------------------------------------------|------------------------------|------------------------------|
|                                                                                     | <b>Normotensive Controls</b> | <b>Hypertensive Patients</b> |

|              | (n=5038)     | (n=10549)    |
|--------------|--------------|--------------|
| <b>AA+AG</b> | 4591 (91.1%) | 9462 (89.7%) |
| <b>GG</b>    | 447 (8.9%)   | 1087 (10.3%) |

Major Allele=A, Minor allele=G. Odds ratio 1.16; 95% confidence interval 0.75-0.95; Fisher's exact p=0.005.

**[00204]** To control for potential confounders that differed between cases and controls (TABLE 9), logistic regression was performed with the recessive genetic model for rs1126478 incorporating age, sex, BMI, and presence of CAD and/or DM2. Results revealed that the homozygous minor allele of rs1126478 remained significantly associated with hypertension after inclusion of these covariates with a similar odds ratio (1.18; p=0.017) (TABLE 10).

| TABLE 10: Logistic regression for LTF SNP rs1126478 with hypertension including covariates. |            |             |         |
|---------------------------------------------------------------------------------------------|------------|-------------|---------|
|                                                                                             | Odds ratio | 95% CI      | P value |
| Intercept                                                                                   |            |             | <0.0001 |
| Age                                                                                         | 1.060      | 1.057-1.063 | <0.0001 |
| BMI                                                                                         | 1.090      | 1.083-1.098 | <0.0001 |
| CAD                                                                                         | 3.896      | 3.343-4.541 | <0.0001 |
| Gender_M                                                                                    | 1.491      | 1.373-1.619 | <0.0001 |
| DM2                                                                                         | 4.872      | 3.976-5.971 | <0.0001 |
| LTF SNP_GG                                                                                  | 1.183      | 1.030-1.360 | 0.017   |

GG=Homozygous minor allele; M=male.

Model: Probability HTN=

$$\frac{1}{1+e^{(-5.425+0.058*AGE+0.087*BMI+1.360*CAD+0.399*GENDER\_M+1.584DM2+0.168*LTF\_SNP\_GG)}}$$

\*\*\*

**[00205]** The foregoing description of the specific aspects will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art, readily modify and/or adapt for various applications such specific aspects, without undue experimentation, without departing from the general concept of the present disclosure. Therefore, such adaptations and modifications are intended to be within the meaning and

range of equivalents of the disclosed aspects, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance.

**[00206]** The breadth and scope of the present disclosure should not be limited by any of the above-described exemplary aspects, but should be defined only in accordance with the following claims and their equivalents.

**[00207]** All publications, patents, patent applications, and/or other documents cited in this application are incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent, patent application, and/or other document were individually indicated to be incorporated by reference for all purposes.

**[00208]** For reasons of completeness, various aspects of the invention are set out in the following numbered clauses:

**[00209]** Clause 1. A method of diagnosing inflammation in a subject being treated for hypertension, the method comprising: (a) obtaining a sample from the subject; (b) determining a level of a biomarker in the sample; (c) comparing the level of the biomarker to a reference level of the biomarker; and (d) identifying the subject as having inflammation when the level of the biomarker is different from the reference level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

**[00210]** Clause 2. The method of clause 1, further comprising determining the level of at least one additional biomarker in the sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4.

**[00211]** Clause 3. The method of clause 2, further comprising comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker; and identifying the subject as having inflammation when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker.

**[00212]** Clause 4. The method of any one of the preceding clauses, wherein the subject is identified as having inflammation when: (a) the level of IL18RAP in the sample is greater than the reference level of IL18RAP; (b) the level of LTF in the sample is greater than the

reference level of LTF; (c) the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1; (d) the level of GZMH in the sample is greater than the reference level of GZMH; (e) the level of ARG1 in the sample is greater than the reference level of ARG1; (f) the level of MMP8 in the sample is greater than the reference level of MMP8; or (g) the level of VSIG4 in the sample is less than the reference level of VSIG4, or any combination of (a)-(g).

**[00213]** Clause 5. A method of determining if a subject being treated for hypertension has or is at risk of developing inflammation, the method comprising: (a) obtaining a sample from the subject; (b) determining a level of a biomarker in the sample; (c) comparing the level of the biomarker to a reference level of the biomarker; and (d) determining the subject has or is at risk of developing inflammation when the level of the biomarker is different from the reference level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

**[00214]** Clause 6. The method of clause 5, further comprising determining the level of at least one additional biomarker in the sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4.

**[00215]** Clause 7. The method of clause 6, further comprising comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker; and identifying the subject as having inflammation when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker.

**[00216]** Clause 8. The method of any one of clauses 5-7, wherein the subject is determined to have or is at risk of developing inflammation when: (a) the level of IL18RAP in the sample is greater than the reference level of IL18RAP; (b) the level of LTF in the sample is greater than the reference level of LTF; (c) the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1; (d) the level of GZMH in the sample is greater than the reference level of GZMH; (e) the level of ARG1 in the sample is greater than the reference level of ARG1; (f) the level of MMP8 in the sample is greater than the reference level of MMP8; or (g) the level of VSIG4 in the sample is less than the reference level of VSIG4, or any combination of (a)-(g).

**[00217]** Clause 9. A method of monitoring progression of inflammation in a subject being treated for hypertension, the method comprising: (a) obtaining first and second samples from the subject; (b) determining a first level of a biomarker in the first sample and a second level

of the biomarker in the second sample; (c) comparing the first and second levels of the biomarker; and (d) determining: (i) inflammation has progressed in the subject when the second level of the biomarker is greater than the first level of the biomarker, or inflammation has not progressed in the subject when the second level of the biomarker is equivalent to or less than the first level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof; or (ii) inflammation has progressed in the subject when the second level of the biomarker is less than the first level of the biomarker, or inflammation has not progressed in the subject when the second level of the biomarker is equivalent to or greater than the first level of the biomarker, wherein the biomarker is VSIG4.

**[00218]** Clause 10. The method of clause 9, further comprising determining a first level of at least one additional biomarker in the first sample and a second level of the at least one additional biomarker in the second sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4.

**[00219]** Clause 11. The method of clause 10, further comprising comparing the first and second levels of the at least one additional biomarker; and determining: (i) inflammation has progressed in the subject when the second level of the additional biomarker is greater than the first level of the additional biomarker, or inflammation has not progressed in the subject when the second level of the additional biomarker is equivalent to or less than the first level of the additional biomarker, wherein the additional biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8; or (ii) inflammation has progressed in the subject when the second level of the additional biomarker is less than the first level of the additional biomarker, or inflammation has not progressed in the subject when the second level of the additional biomarker is equivalent to or greater than the first level of the additional biomarker, wherein the additional biomarker is VSIG4.

**[00220]** Clause 12. A method of determining if a subject being treated for hypertension would benefit from anti-inflammatory therapy, the method comprising: (a) obtaining a sample from the subject; (b) determining a level of a biomarker in the sample; (c) comparing the level of the biomarker to a reference level of the biomarker; and (d) determining that the subject would benefit from anti-inflammatory therapy when the level of the biomarker is different from the reference level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

**[00221]** Clause 13. The method of clause 12, further comprising determining the level of at least one additional biomarker in the sample, wherein the at least one additional

biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4.

**[00222]** Clause 14. The method of clause 13, further comprising comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker; and determining that the subject would benefit from anti-inflammatory therapy when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker.

**[00223]** Clause 15. The method of any one of clauses 12-14, wherein the subject is determined to likely benefit from anti-inflammatory therapy when: (a) the level of IL18RAP in the sample is greater than the reference level of IL18RAP; (b) the level of LTF in the sample is greater than the reference level of LTF; (c) the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1; (d) the level of GZMH in the sample is greater than the reference level of GZMH; (e) the level of ARG1 in the sample is greater than the reference level of ARG1; (f) the level of MMP8 in the sample is greater than the reference level of MMP8; or (g) the level of VSIG4 in the sample is less than the reference level of VSIG4, or any combination of (a)-(g).

**[00224]** Clause 16. A method of monitoring a subject's response to anti-inflammatory therapy, wherein the subject is being co-treated for hypertension, the method comprising: (a) obtaining first and second samples from the subject; (b) determining a first level of a biomarker in the first sample and a second level of the biomarker in the second sample; (c) comparing the first and second levels of the biomarker; and (d) determining: (i) the subject is not responding to the anti-inflammatory therapy when the second level of the biomarker is greater than the first level of the biomarker, or subject is responding to the anti-inflammatory therapy when the second level of the biomarker is equivalent to or less than the first level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof; or (ii) the subject is not responding to the anti-inflammatory therapy when the second level of the biomarker is less than the first level of the biomarker, or the subject is responding to the anti-inflammatory therapy when the second level of the biomarker is equivalent to or greater than the first level of the biomarker, wherein the biomarker is VSIG4.

**[00225]** Clause 17. The method of clause 16, further comprising determining a first level of at least one additional biomarker in the first sample and a second level of the at least one additional biomarker in the second sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4.

**[00226]** Clause 18. The method of clause 17, further comprising comparing the first and second levels of the at least one additional biomarker; and determining: (i) the subject is not responding to the anti-inflammatory therapy when the second level of the additional biomarker is greater than the first level of the additional biomarker, or the subject is responding to the anti-inflammatory therapy when the second level of the additional biomarker is equivalent to or less than the first level of the additional biomarker, wherein the additional biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8; or (ii) the subject is not responding to the anti-inflammatory therapy when the second level of the additional biomarker is less than the first level of the additional biomarker, or the subject is responding to the anti-inflammatory therapy when the second level of the additional biomarker is equivalent to or greater than the first level of the additional biomarker, wherein the additional biomarker is VSIG4.

**[00227]** Clause 19. A method of diagnosing hypertension in a subject, the method comprising: (a) obtaining a sample from the subject; (b) determining a level of a biomarker in the sample; (c) comparing the level of the biomarker to a reference level of the biomarker; and (d) identifying the subject as having hypertension when the level of the biomarker is different from the reference level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

**[00228]** Clause 20. The method of clause 19, further comprising determining the level of at least one additional biomarker in the sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4.

**[00229]** Clause 21. The method of clause 20, further comprising comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker; and identifying the subject as having hypertension when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker.

**[00230]** Clause 22. The method of any one of clauses 19-21, wherein the subject is identified as having hypertension when: (a) the level of IL18RAP in the sample is greater than the reference level of IL18RAP; (b) the level of LTF in the sample is greater than the reference level of LTF; (c) the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1; (d) the level of GZMH in the sample is greater than the reference level of GZMH; (e) the level of ARG1 in the sample is greater than the reference level of ARG1; (f) the level of MMP8 in the sample is greater than the reference level of MMP8; or (g) the level

of VSIG4 in the sample is less than the reference level of VSIG4, or any combination of (a)-(g).

**[00231]** Clause 23. The method of any one of the preceding clauses, wherein the level of the biomarker in the sample is greater than the reference level of the biomarker, and wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof.

**[00232]** Clause 24. The method of any one of the preceding clauses, wherein the level of the biomarker in the sample is less than the reference level of the biomarker, and wherein the biomarker is VSIG4.

**[00233]** Clause 25. The method of any one of the preceding clauses, wherein the sample is a biological sample.

**[00234]** Clause 26. The method of any one of the preceding clauses, wherein the sample is selected from whole blood, serum, and plasma.

**[00235]** Clause 27. The method of any one of the above clauses, wherein the sample comprises monocytes.

**[00236]** Clause 28. The method of any one of the preceding clauses, wherein determining the level of the biomarker in the sample includes detecting the biomarker with a technique selected from immunoassay, sequencing, and hybridization, or a combination thereof.

**[00237]** Clause 29. The method of any one of the preceding clauses, wherein the reference level of the biomarker is the level of the biomarker in a control sample.

**[00238]** Clause 30. The method of any one of clauses 1-29, wherein the reference level of the biomarker is a cutoff level.

**[00239]** Clause 31. The method of clause 30, wherein the cutoff value is determined by a receiver operating curve (ROC) analysis from biological samples of a patient group.

**[00240]** Clause 32. The method of clause 30, wherein the cutoff level is determined by a mean plus 2 standard deviation analysis of multiple control samples.

**[00241]** Clause 33. The method of any one of the preceding clauses, wherein the subject is hypertensive.

**[00242]** Clause 34. The method of any one of the preceding clauses, further comprising administering an anti-inflammation therapy to the subject.

**[00243]** Clause 35. The method of any one of the preceding clauses, further comprising administering an anti-hypertension therapy to the subject.

**[00244]** Clause 36. A method of treating inflammation in a subject being treated for hypertension, the method comprising inhibiting the transcription, expression, or activity of, or a combination thereof, a gene or gene product selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof, or increasing the transcription, expression, or activity of, or a combination thereof, a gene or gene product selected from VSIG4.

**[00245]** Clause 37. A method of treating hypertension in a subject, the method comprising inhibiting the transcription, expression, or activity of, or a combination thereof, a gene or gene product selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof, or increasing the transcription, expression, or activity of, or a combination thereof, a gene or gene product selected from VSIG4.

**[00246]** Clause 38. A kit for detecting inflammation in a subject being treated for hypertension, the kit comprising one or more reagents for detecting a biomarker selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

**[00247]** Clause 39. A kit for detecting hypertension in a subject, the kit comprising one or more reagents for detecting a biomarker selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

**[00248]** Clause 40. A composition comprising a probe array for detecting a biomarker in a sample, the array comprising a plurality of probes that hybridizes to one or more biomarkers selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

**[00249]** Clause 41. The composition of clause 40, further comprising a solid support with the plurality of probes attached thereto.

## SEQUENCES

SEQ ID NO: 1

IL18RAP polynucleotide

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LTF polynucleotide

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93

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SEQ ID NO: 4

GZMH polynucleotide

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SEQ ID NO: 5

ARG1 polynucleotide

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SEQ ID NO: 6

MMP8 polynucleotide

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SEQ ID NO: 7

VSI4 polynucleotide

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 AGGAGCCACACATCCAGGGACGCTGCTCCATAAGAGCTAAGGACTCCCAGGGATATCT  
 CAAAGTCATTAATCTTA

SEQ ID NO: 8

IL18RAP protein, Accession No. AAI06765, 457 amino acids

MILEVKPQTNASCEYSASHKQDLLLGSTGSISCPSLSCQSDAQSPAVTWYKNGKLLSVERS  
 NRIVVDEVYDYHQGTIVCDYTQSDTVSSWTVRVVQVTVGDTKLKPDILDPVEDTLEVEL  
 GKPLTISCKARFGFERVFNPNVIKWKYKDSLEWEVSVPEAKSIKSTLKDEIERNIIEKVTRD  
 LRRKFVCFVQNSIGNTTQSVQLKEKRGVLLYILLGTIGTLVAVLAASALLYRHWEIVLLYRT  
 YQSKDQTLGDKKDFDAFVSYAKWSSFPSEATSSLSEEHLALSFPDVLENKYGYSLCLLER  
 DVAPGGVYAEDIVSIKRSRRGIFILSPNYVNGPSIFELQAAVNLAALDDQTLKLILIKFCYFQEP  
 ESLPHLVKKALRVLPVTWVRLKSVPPNSRFWAKMRYHMPVKNSQGFTWNQLRITSRIFQ  
 WKGLSRTETTGRSSQPKWEV

SEQ ID NO: 9

LTF protein, Accession No. EAW64767, 711 amino acids

MKLVFLVLLF LGALGLCLAG RRRRSVQWCA VSQPEATKCF QWQRNMRKVR  
 GPPVSCIKRD  
 SPIQCIQAIA ENRADAVTLD GGFIYEAGLA PYKLRPVAAE VYGTERQPRT HYYAVAVVKK  
 GGSFQLNELQ GLKSCHTGLR RTAGWNVPIG TLRPFLNWTG PPEPIEAAVA  
 RFFSASCVP  
 ADKGQFPNLC RLCAGTGENK CAFSSQEPYF SYSGAFKCLR DGAGDVAFIR  
 ESTVFEDLSD  
 EAERDEYELL CPDNTRKPVD KFKDCHLARV PSHAVVARSV NGKEDAIWNL  
 LRQAQEKFGK  
 DKSPKFQLFG SPSGQKDLLF KDSAIGFSRV PPRIDSGLYL GSGYFTAIQN LRKSEEEVAA  
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 LAMAPNHAVV SRMDKVERLK QVLLHQQAKF GRNGSDCPDK  
 FCLFQSETKNLLFNDNTECL ARLHGKTTYE KYLGPQYVAG ITNLKKCSTS PLLEACEFLR  
 K

SEQ ID NO: 10

PGLYRP1 protein, Accession No. AAH96156, 196 amino acids

MSRRSMLLAW ALPSLLRLGA AQETEDPACC SPIVPRNEWK ALASECAQHL  
 SLPLRYVVVS  
 HTAGSSCNTP ASCQQQARNV QHYHMKTLGW CDVGYNFLIG EDGLVYEGRG  
 WNFTGAHSGHLWNPMISIGS FMGNVMDRVP TPQAIRAAQG LLACGVAQGA  
 LRSNYVLKGH RDVQRTLSPGNQLYHLIQNW PHYRSP

SEQ ID NO: 11

GZMH protein, Accession No. AAH27974, 246 amino acids

MQPFLLLLAF LLTPGAGTEE IIGGHEAKPH SRPYMAFVQF LQEKSRKRCG GILVRKDFVL  
TAAHCQGSSI NVTLGAHNIK EQERTQQFIP VKRPIHPAY NPKNFSNDIM LLQLERKAKW  
TTAVRPLRLP SSKAQVKPGQ LCSVAGWGYV SMSTLATTLO EVLLTVQKDC  
QCERLFHGNV  
SRATEICVGD PKKTQTGFKG DSGGPLVCKD VAQGILSYGN KKGTPPGVYI  
KVSHFLPWIK  
RTMKRL

SEQ ID NO: 12

ARG1 protein, Accession No. AAH05321, 236 amino acids

MSAKSRTIGI IGAPFSKGQP RGGVEEGPTV LRKAGLLEKL KEQECDVKDY GDLPPADIPN  
DSPFQIVKNP RSVGKASEQL AGKVAEVKKK GRISLVGGD HSLAIGSIG HARVHPDLGV  
IWVDAHTDIN TPLTTTSGNL HGQPVSFLLK ELKGKIPDVP GFSWVTPCIS AKDIVYIGLR  
DVDPGEHYIL KTLGIKYFSM TEVTRTVNTA VAITLACFGL AREGNHKKPID YLNPPK

SEQ ID NO: 13

MMP8 protein, Accession No. EAW67027, 467 amino acids

MFSKLTLPFL LLLHVQISKA FPVSSKEKNT KIVQDYLEKF YQLPSNQYQS TRKNGTNVIV  
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KSSGAFPGI  
ESKVDVAFQQ EHFFHVFSGP RYYAFDLIAQ RVTRVARGNK WLNCRYG

SEQ ID NO: 14

VSIG4 protein, Accession No. AIC50863, 399 amino acids

MGILLGLLLL GHLTVDITYGR PILEVPESVT GPWKGDVNLP CTYDPLQGYT  
QVLVKWLVQR  
GSDPVTIFLR DSSGDHIQQA KYQGRLHVSH KVPGDVSLQL STLEMDDRSH  
YTCEVTWQTP  
DGNQVVRDKI TELRVQKLSV SKPTVTTGSG YGFTVPQGM R ISLQCQARGS  
PPISYIWKQ  
QTNNQEPIKV ATLSTLLFKP AVIADSGSYF CTAKGQVGSE QHSDIVKFVV KDSSKLLKTK  
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MAYIMLCRKT SQQEHVYEA RAHAREANDS GETMRVAIFA SGCSSDEPTS  
QNLGNNYSDE  
PCIGQEYQII AQINGNYARL LDTVPLDYEF LATEGKSVC

## CLAIMS

We claim:

1. A method of diagnosing inflammation in a subject being treated for hypertension, the method comprising:

- (a) obtaining a sample from the subject;
- (b) determining a level of a biomarker in the sample;
- (c) comparing the level of the biomarker to a reference level of the biomarker;

and

(d) identifying the subject as having inflammation when the level of the biomarker is different from the reference level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

2. The method of claim 1, further comprising determining the level of at least one additional biomarker in the sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4.

3. The method of claim 2, further comprising comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker; and identifying the subject as having inflammation when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker.

4. The method of any one of the preceding claims, wherein the subject is identified as having inflammation when:

- (a) the level of IL18RAP in the sample is greater than the reference level of IL18RAP;
- (b) the level of LTF in the sample is greater than the reference level of LTF;
- (c) the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1;
- (d) the level of GZMH in the sample is greater than the reference level of GZMH;
- (e) the level of ARG1 in the sample is greater than the reference level of ARG1;
- (f) the level of MMP8 in the sample is greater than the reference level of MMP8;

or

(g) the level of VSIG4 in the sample is less than the reference level of VSIG4, or any combination of (a)-(g).

5. A method of determining if a subject being treated for hypertension has or is at risk of developing inflammation, the method comprising:

- (a) obtaining a sample from the subject;
- (b) determining a level of a biomarker in the sample;
- (c) comparing the level of the biomarker to a reference level of the biomarker;

and

(d) determining the subject has or is at risk of developing inflammation when the level of the biomarker is different from the reference level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

6. The method of claim 5, further comprising determining the level of at least one additional biomarker in the sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4.

7. The method of claim 6, further comprising comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker; and identifying the subject as having inflammation when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker.

8. The method of any one of claims 5-7, wherein the subject is determined to have or is at risk of developing inflammation when:

- (a) the level of IL18RAP in the sample is greater than the reference level of IL18RAP;
- (b) the level of LTF in the sample is greater than the reference level of LTF;
- (c) the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1;
- (d) the level of GZMH in the sample is greater than the reference level of GZMH;
- (e) the level of ARG1 in the sample is greater than the reference level of ARG1;
- (f) the level of MMP8 in the sample is greater than the reference level of MMP8;

or

(g) the level of VSIG4 in the sample is less than the reference level of VSIG4, or any combination of (a)-(g).

9. A method of monitoring progression of inflammation in a subject being treated for hypertension, the method comprising:

- (a) obtaining first and second samples from the subject;

(b) determining a first level of a biomarker in the first sample and a second level of the biomarker in the second sample;

(c) comparing the first and second levels of the biomarker; and

(d) determining:

(i) inflammation has progressed in the subject when the second level of the biomarker is greater than the first level of the biomarker, or inflammation has not progressed in the subject when the second level of the biomarker is equivalent to or less than the first level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof; or

(ii) inflammation has progressed in the subject when the second level of the biomarker is less than the first level of the biomarker, or inflammation has not progressed in the subject when the second level of the biomarker is equivalent to or greater than the first level of the biomarker, wherein the biomarker is VSIG4.

10. The method of claim 9, further comprising determining a first level of at least one additional biomarker in the first sample and a second level of the at least one additional biomarker in the second sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4.

11. The method of claim 10, further comprising comparing the first and second levels of the at least one additional biomarker; and determining:

(i) inflammation has progressed in the subject when the second level of the additional biomarker is greater than the first level of the additional biomarker, or inflammation has not progressed in the subject when the second level of the additional biomarker is equivalent to or less than the first level of the additional biomarker, wherein the additional biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8; or

(ii) inflammation has progressed in the subject when the second level of the additional biomarker is less than the first level of the additional biomarker, or inflammation has not progressed in the subject when the second level of the additional biomarker is equivalent to or greater than the first level of the additional biomarker, wherein the additional biomarker is VSIG4.

12. A method of determining if a subject being treated for hypertension would benefit from anti-inflammatory therapy, the method comprising:

(a) obtaining a sample from the subject;

(b) determining a level of a biomarker in the sample;

(c) comparing the level of the biomarker to a reference level of the biomarker;  
and

(d) determining that the subject would benefit from anti-inflammatory therapy when the level of the biomarker is different from the reference level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

13. The method of claim 12, further comprising determining the level of at least one additional biomarker in the sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4.

14. The method of claim 13, further comprising comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker; and determining that the subject would benefit from anti-inflammatory therapy when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker.

15. The method of any one of claims 12-14, wherein the subject is determined to likely benefit from anti-inflammatory therapy when:

- (a) the level of IL18RAP in the sample is greater than the reference level of IL18RAP;
- (b) the level of LTF in the sample is greater than the reference level of LTF;
- (c) the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1;
- (d) the level of GZMH in the sample is greater than the reference level of GZMH;
- (e) the level of ARG1 in the sample is greater than the reference level of ARG1;
- (f) the level of MMP8 in the sample is greater than the reference level of MMP8;

or

- (g) the level of VSIG4 in the sample is less than the reference level of VSIG4, or any combination of (a)-(g).

16. A method of monitoring a subject's response to anti-inflammatory therapy, wherein the subject is being co-treated for hypertension, the method comprising:

- (a) obtaining first and second samples from the subject;
- (b) determining a first level of a biomarker in the first sample and a second level of the biomarker in the second sample;
- (c) comparing the first and second levels of the biomarker; and

(d) determining:

(i) the subject is not responding to the anti-inflammatory therapy when the second level of the biomarker is greater than the first level of the biomarker, or subject is responding to the anti-inflammatory therapy when the second level of the biomarker is equivalent to or less than the first level of the biomarker, wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof; or

(ii) the subject is not responding to the anti-inflammatory therapy when the second level of the biomarker is less than the first level of the biomarker, or the subject is responding to the anti-inflammatory therapy when the second level of the biomarker is equivalent to or greater than the first level of the biomarker, wherein the biomarker is VSIG4.

17. The method of claim 16, further comprising determining a first level of at least one additional biomarker in the first sample and a second level of the at least one additional biomarker in the second sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4.

18. The method of claim 17, further comprising comparing the first and second levels of the at least one additional biomarker; and determining:

(i) the subject is not responding to the anti-inflammatory therapy when the second level of the additional biomarker is greater than the first level of the additional biomarker, or the subject is responding to the anti-inflammatory therapy when the second level of the additional biomarker is equivalent to or less than the first level of the additional biomarker, wherein the additional biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8; or

(ii) the subject is not responding to the anti-inflammatory therapy when the second level of the additional biomarker is less than the first level of the additional biomarker, or the subject is responding to the anti-inflammatory therapy when the second level of the additional biomarker is equivalent to or greater than the first level of the additional biomarker, wherein the additional biomarker is VSIG4.

19. A method of diagnosing hypertension in a subject, the method comprising:

(a) obtaining a sample from the subject;

(b) determining a level of a biomarker in the sample;

(c) comparing the level of the biomarker to a reference level of the biomarker;

and

(d) identifying the subject as having hypertension when the level of the biomarker is different from the reference level of the biomarker,

wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

20. The method of claim 19, further comprising determining the level of at least one additional biomarker in the sample, wherein the at least one additional biomarker is selected from the other of IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4.

21. The method of claim 20, further comprising comparing the level of the at least one additional biomarker to a reference level of the at least one additional biomarker; and identifying the subject as having hypertension when the level of the at least one additional biomarker is different from the reference level of the at least one additional biomarker.

22. The method of any one of claims 19-21, wherein the subject is identified as having hypertension when:

(a) the level of IL18RAP in the sample is greater than the reference level of IL18RAP;

(b) the level of LTF in the sample is greater than the reference level of LTF;

(c) the level of PGLYRP1 in the sample is greater than the reference level of PGLYRP1;

(d) the level of GZMH in the sample is greater than the reference level of GZMH;

(e) the level of ARG1 in the sample is greater than the reference level of ARG1;

(f) the level of MMP8 in the sample is greater than the reference level of MMP8;

or

(g) the level of VSIG4 in the sample is less than the reference level of VSIG4, or any combination of (a)-(g).

23. The method of any one of the preceding claims, wherein the level of the biomarker in the sample is greater than the reference level of the biomarker, and wherein the biomarker is selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof.

24. The method of any one of the preceding claims, wherein the level of the biomarker in the sample is less than the reference level of the biomarker, and wherein the biomarker is VSIG4.

25. The method of any one of the preceding claims, wherein the sample is a biological sample.
26. The method of any one of the preceding claims, wherein the sample is selected from whole blood, serum, and plasma.
27. The method of any one of the above claims, wherein the sample comprises monocytes.
28. The method of any one of the preceding claims, wherein determining the level of the biomarker in the sample includes detecting the biomarker with a technique selected from immunoassay, sequencing, and hybridization, or a combination thereof.
29. The method of any one of the preceding claims, wherein the reference level of the biomarker is the level of the biomarker in a control sample.
30. The method of any one of claims 1-29, wherein the reference level of the biomarker is a cutoff level.
31. The method of claim 30, wherein the cutoff value is determined by a receiver operating curve (ROC) analysis from biological samples of a patient group.
32. The method of claim 30, wherein the cutoff level is determined by a mean plus 2 standard deviation analysis of multiple control samples.
33. The method of any one of the preceding claims, wherein the subject is hypertensive.
34. The method of any one of the preceding claims, further comprising administering an anti-inflammation therapy to the subject.
35. The method of any one of the preceding claims, further comprising administering an anti-hypertension therapy to the subject.
36. A method of treating inflammation in a subject being treated for hypertension, the method comprising inhibiting the transcription, expression, or activity of, or a combination thereof, a gene or gene product selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1,

and MMP8, or a combination thereof, or increasing the transcription, expression, or activity of, or a combination thereof, a gene or gene product selected from VSIG4.

37. A method of treating hypertension in a subject, the method comprising inhibiting the transcription, expression, or activity of, or a combination thereof, a gene or gene product selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, and MMP8, or a combination thereof, or increasing the transcription, expression, or activity of, or a combination thereof, a gene or gene product selected from VSIG4.

38. A kit for detecting inflammation in a subject being treated for hypertension, the kit comprising one or more reagents for detecting a biomarker selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

39. A kit for detecting hypertension in a subject, the kit comprising one or more reagents for detecting a biomarker selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

40. A composition comprising a probe array for detecting a biomarker in a sample, the array comprising a plurality of probes that hybridizes to one or more biomarkers selected from IL18RAP, LTF, PGLYRP1, GZMH, ARG1, MMP8, and VSIG4, or a combination thereof.

41. The composition of claim 40, further comprising a solid support with the plurality of probes attached thereto.

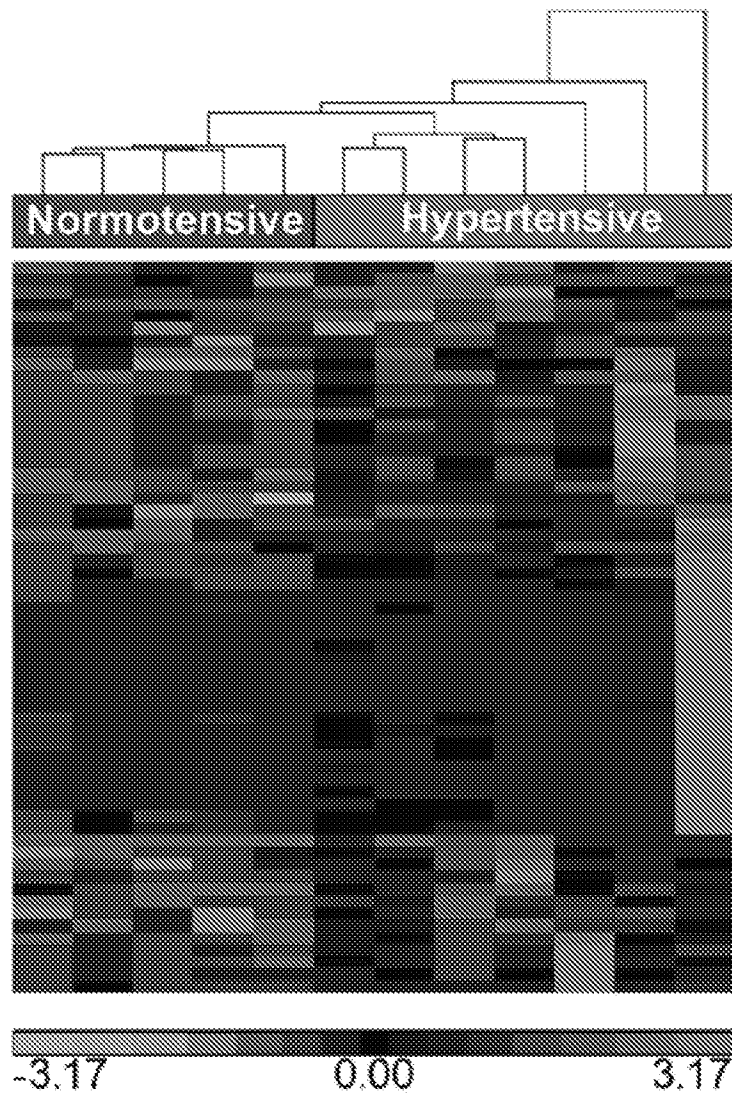


FIG. 1A

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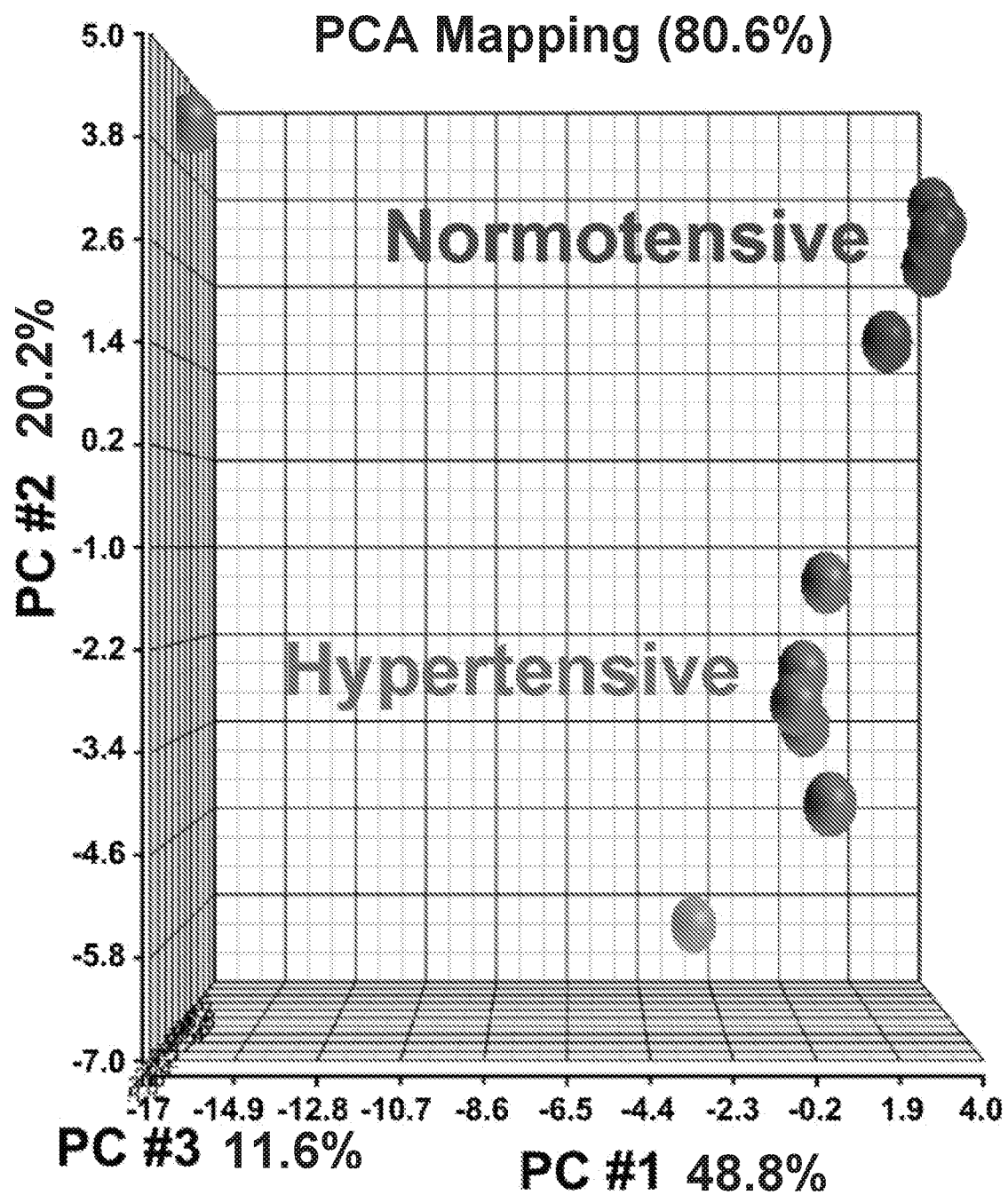


FIG. 1B

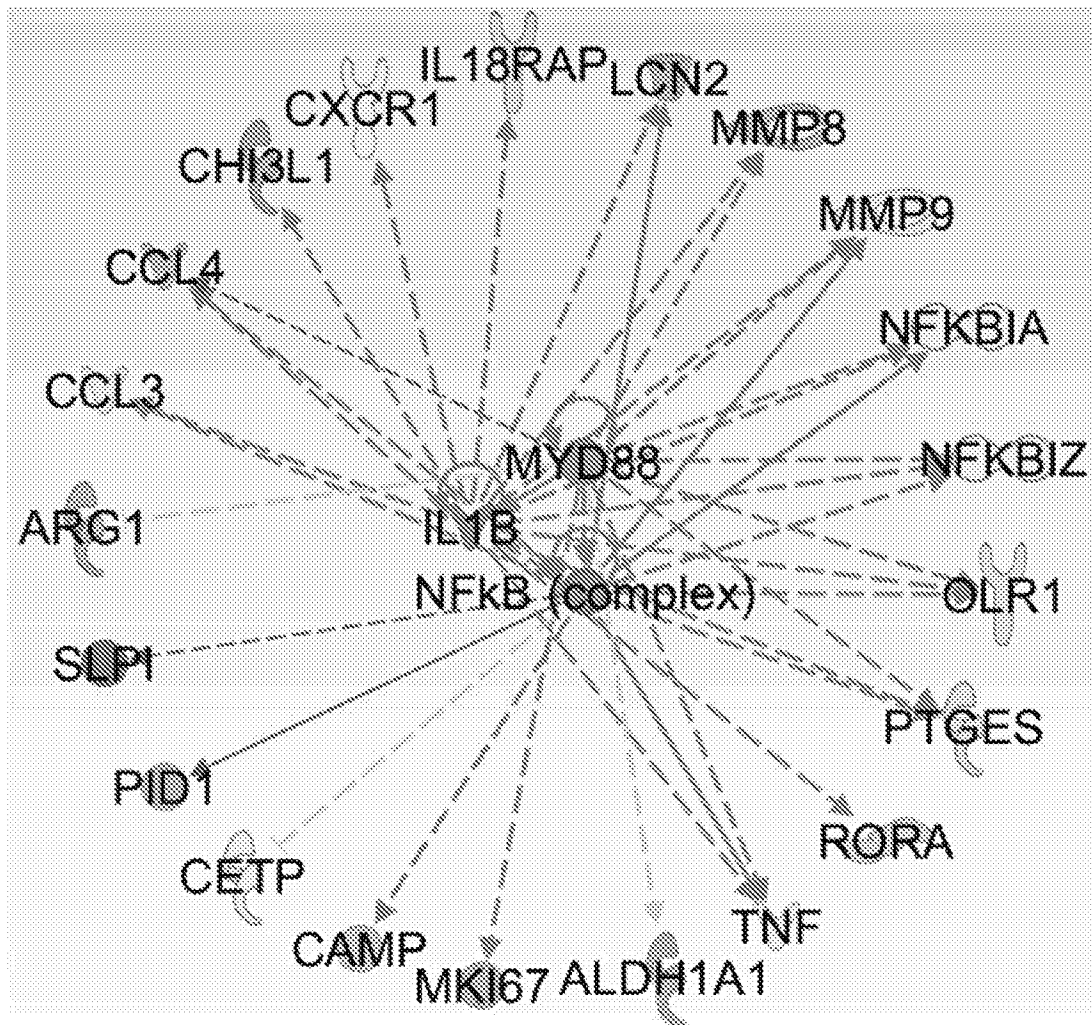


FIG. 1C

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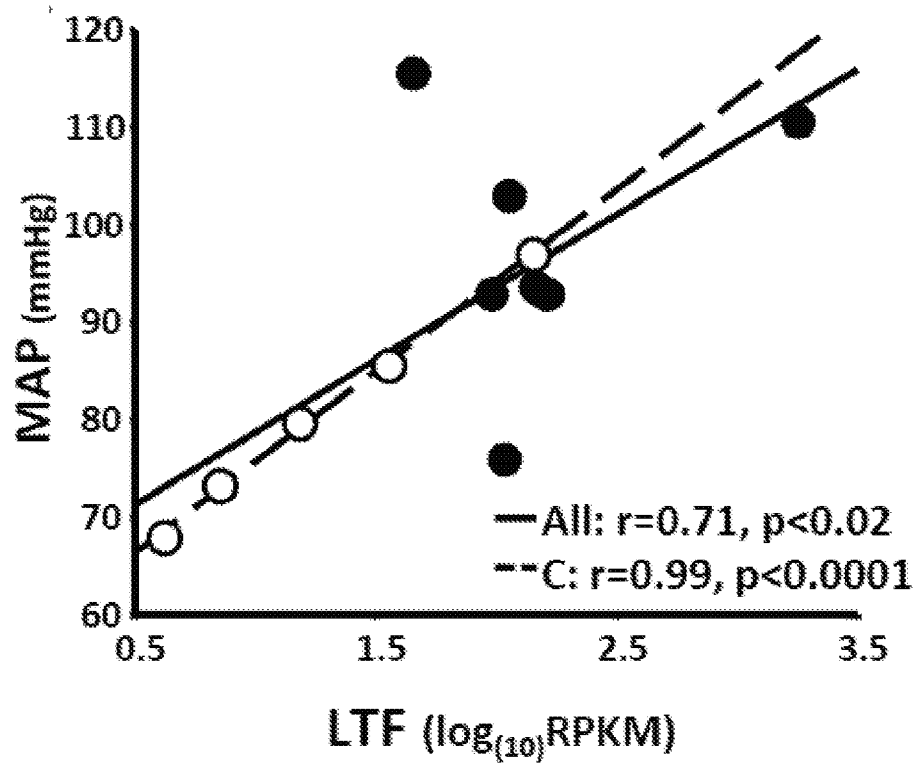


FIG. 2A

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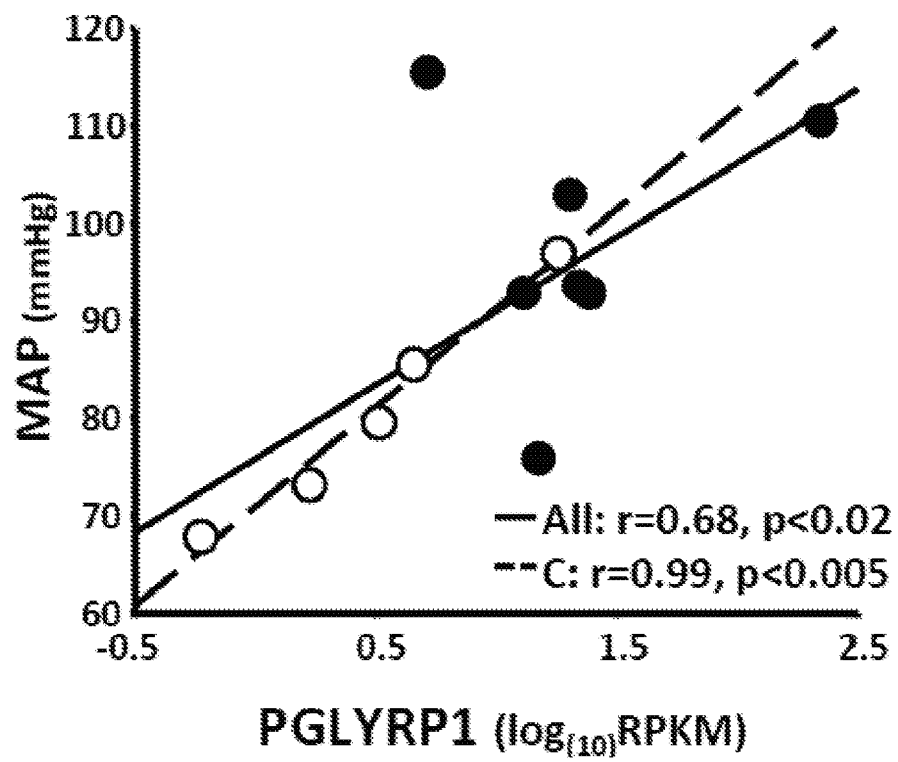


FIG. 2B

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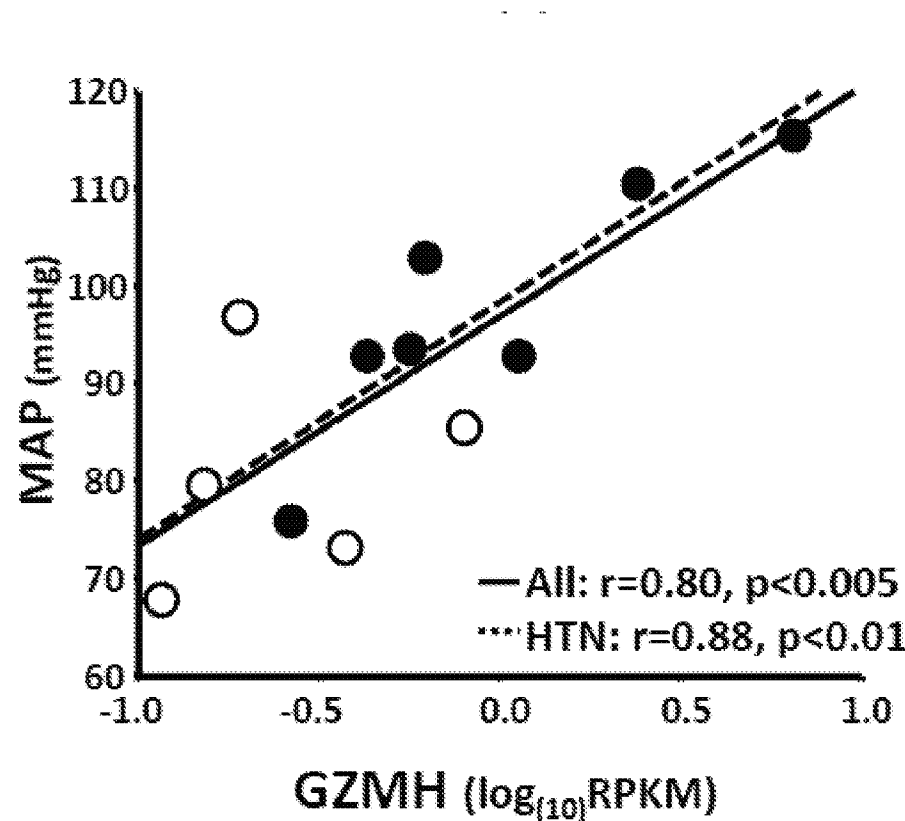


FIG. 2C

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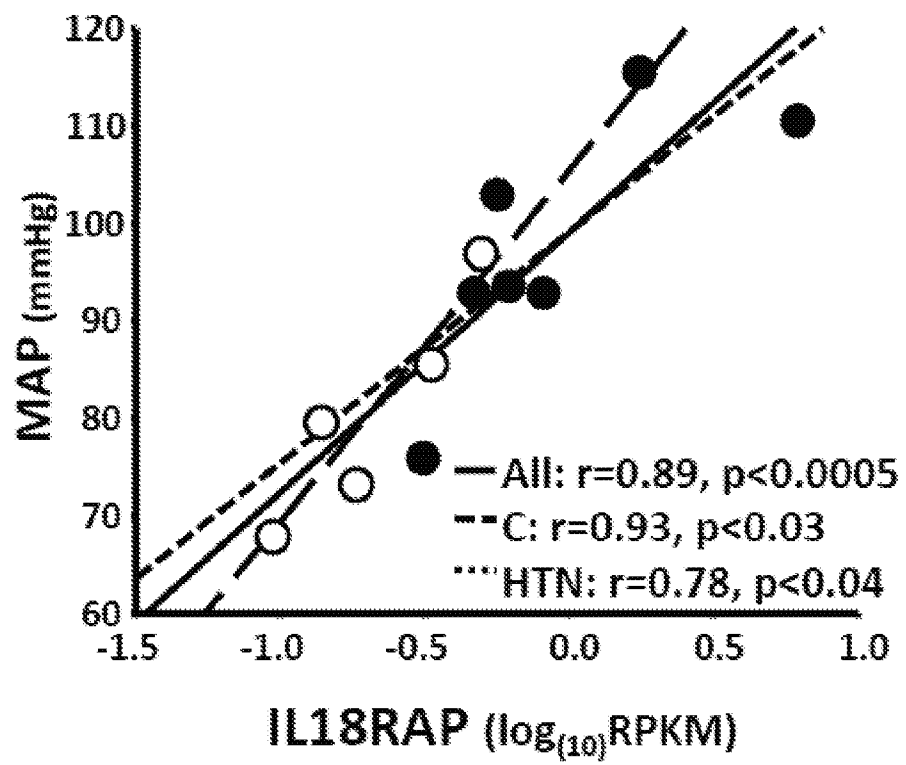


FIG. 2D

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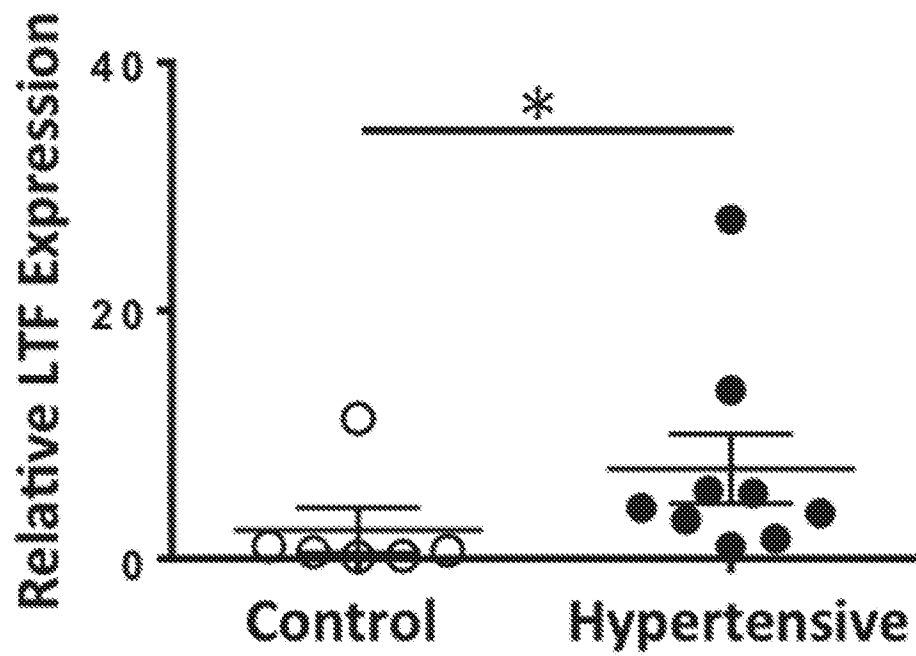


FIG. 3A

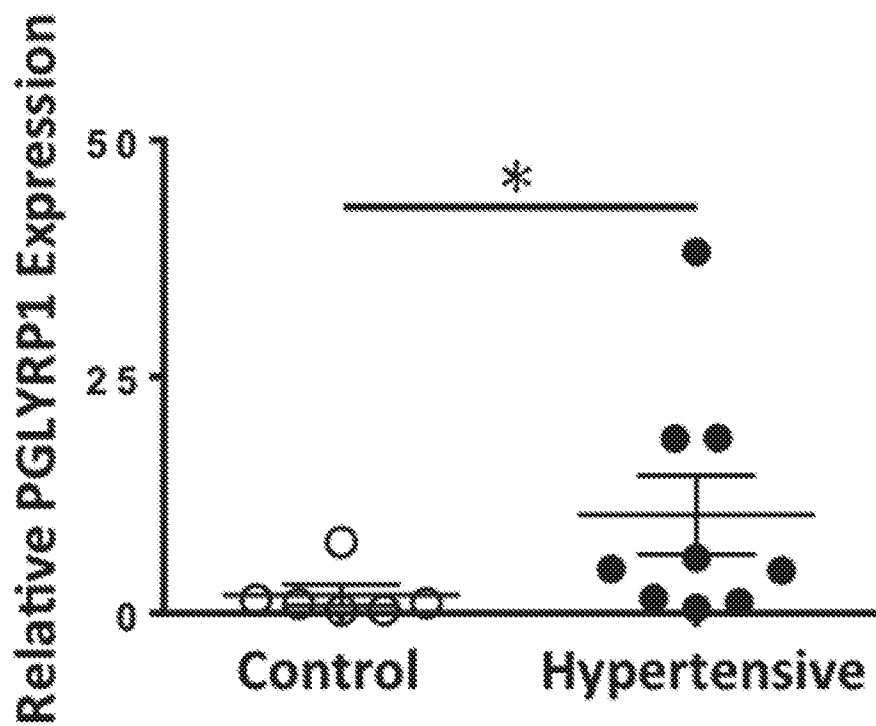


FIG. 3B

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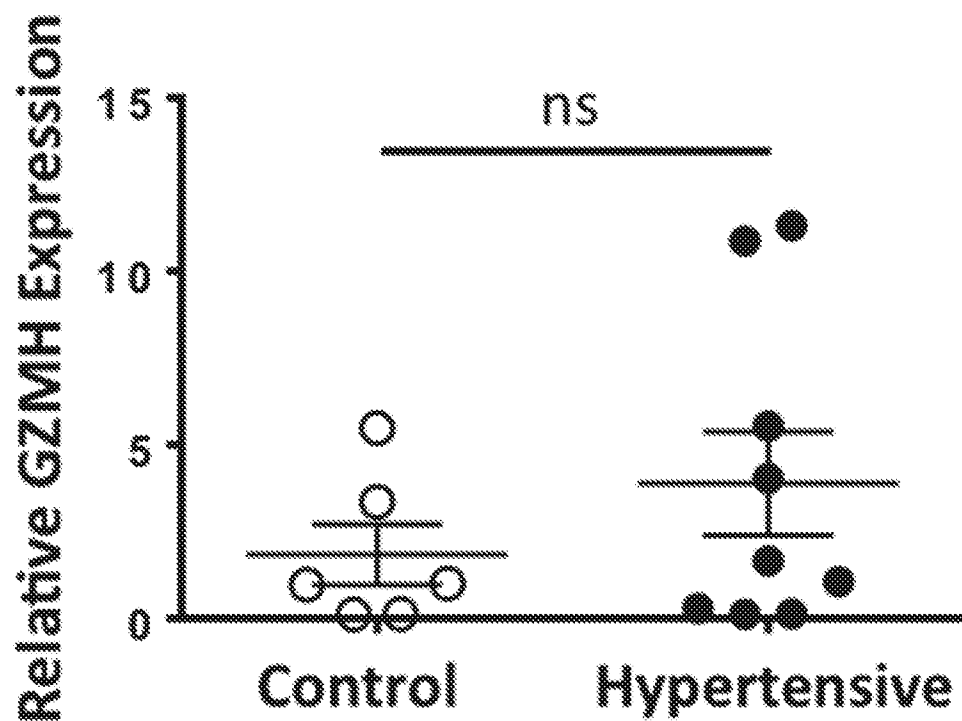


FIG. 3C

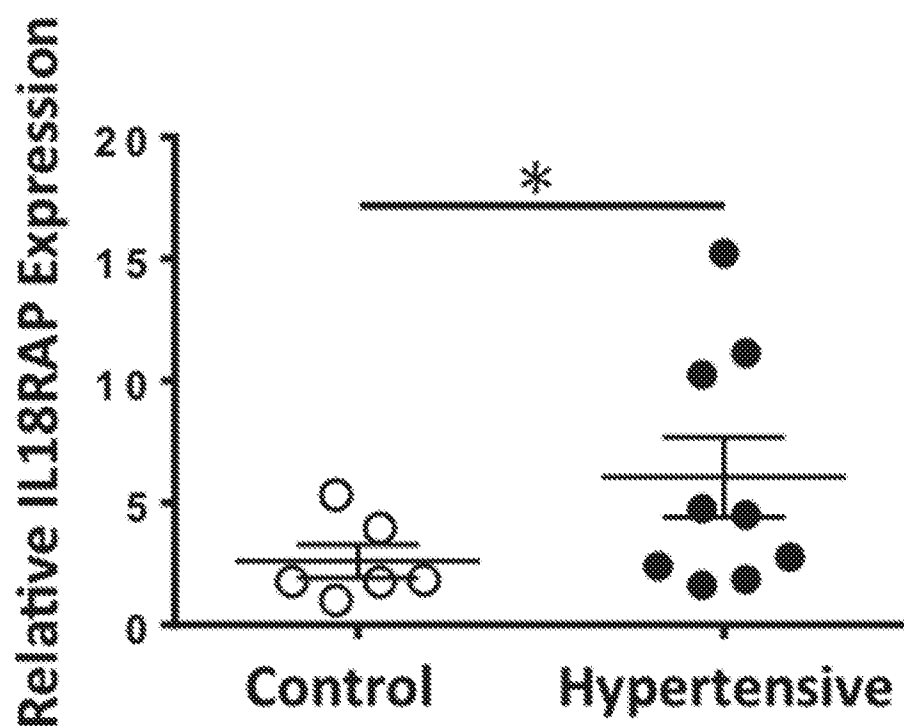


FIG. 3D

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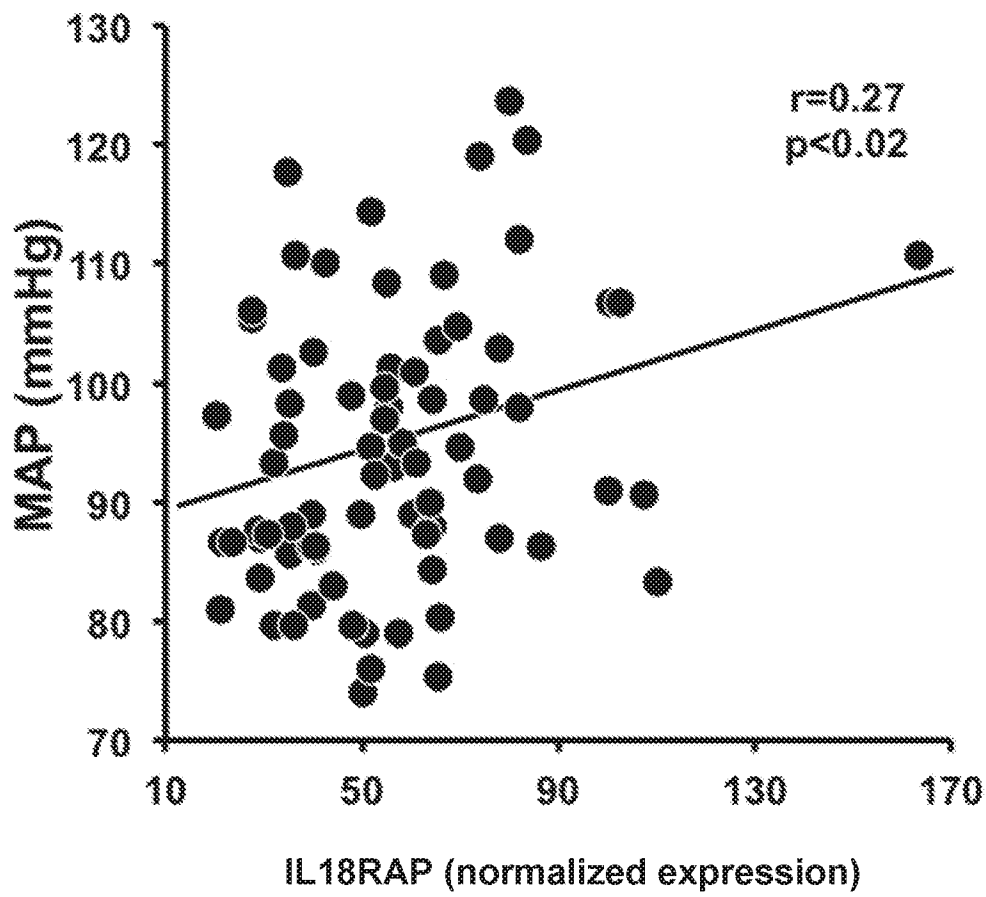


FIG. 4A

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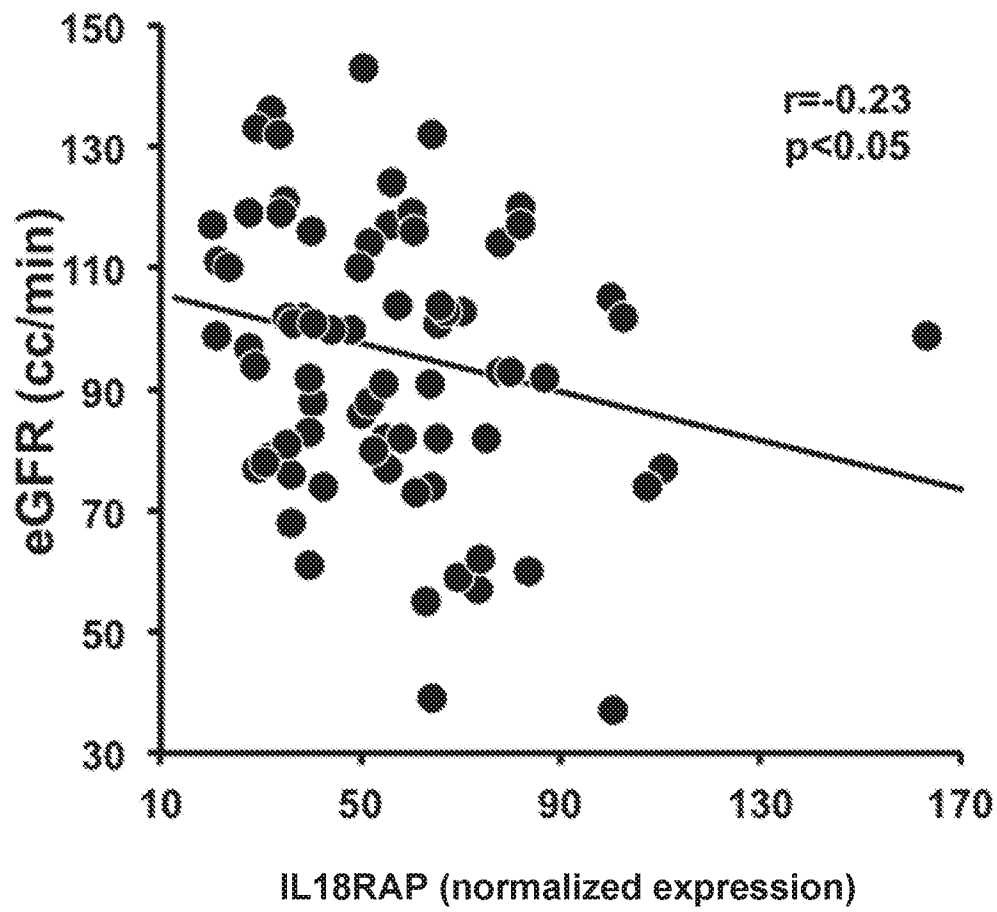


FIG. 4B

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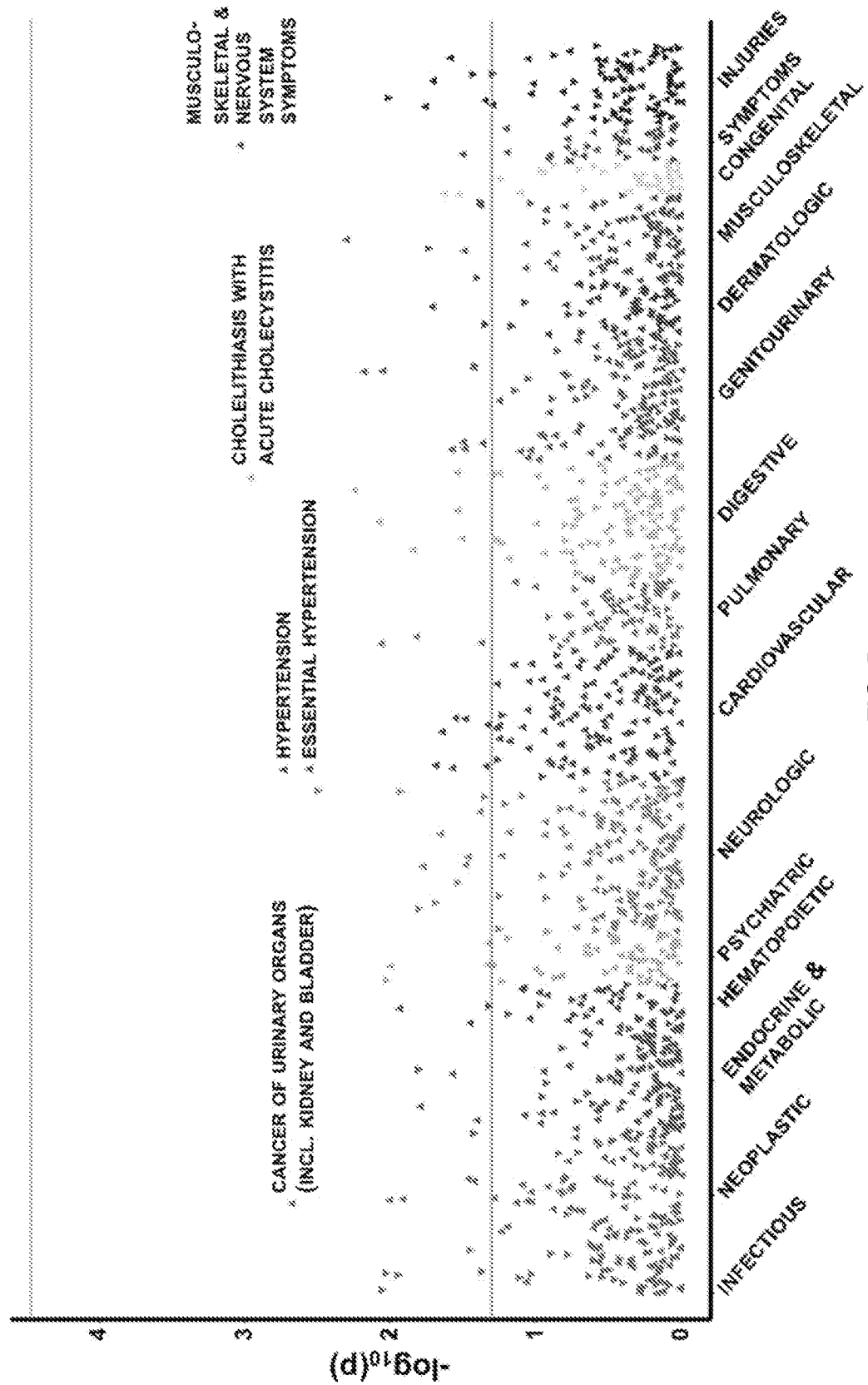


FIG. 5

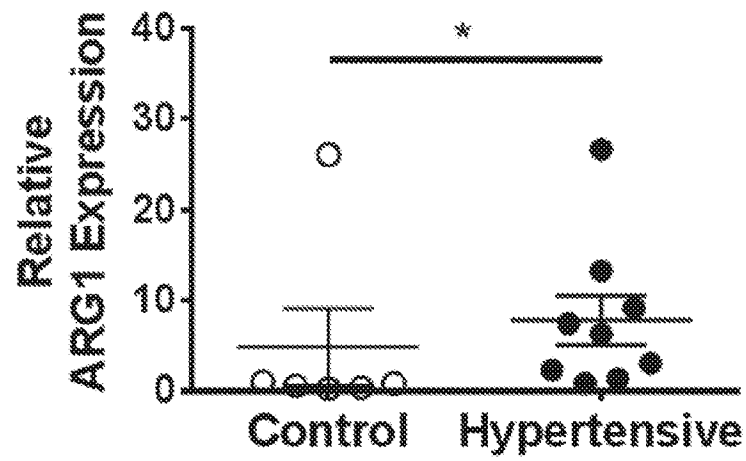


FIG. 6A

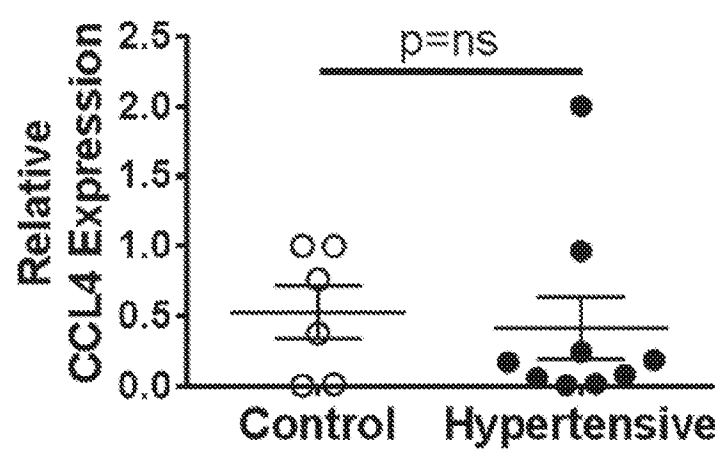


FIG. 6B

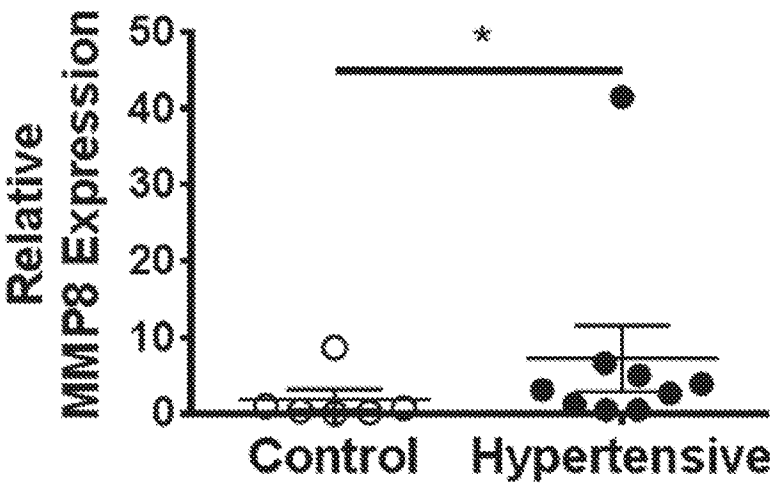


FIG. 6C

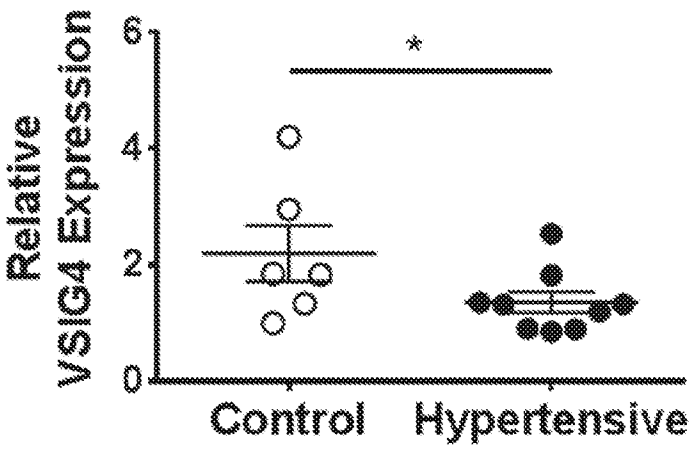


FIG. 6D

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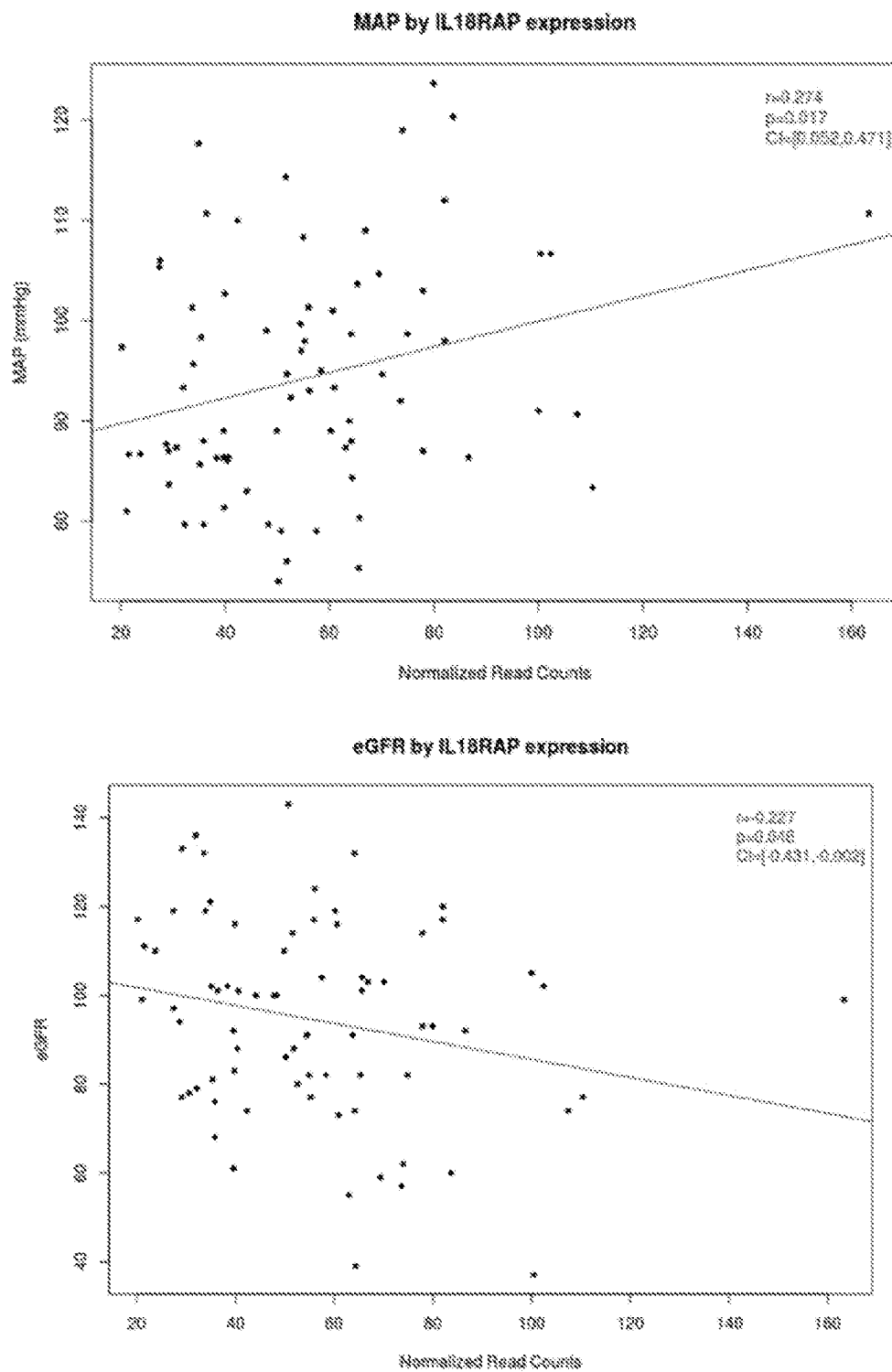


FIG. 7

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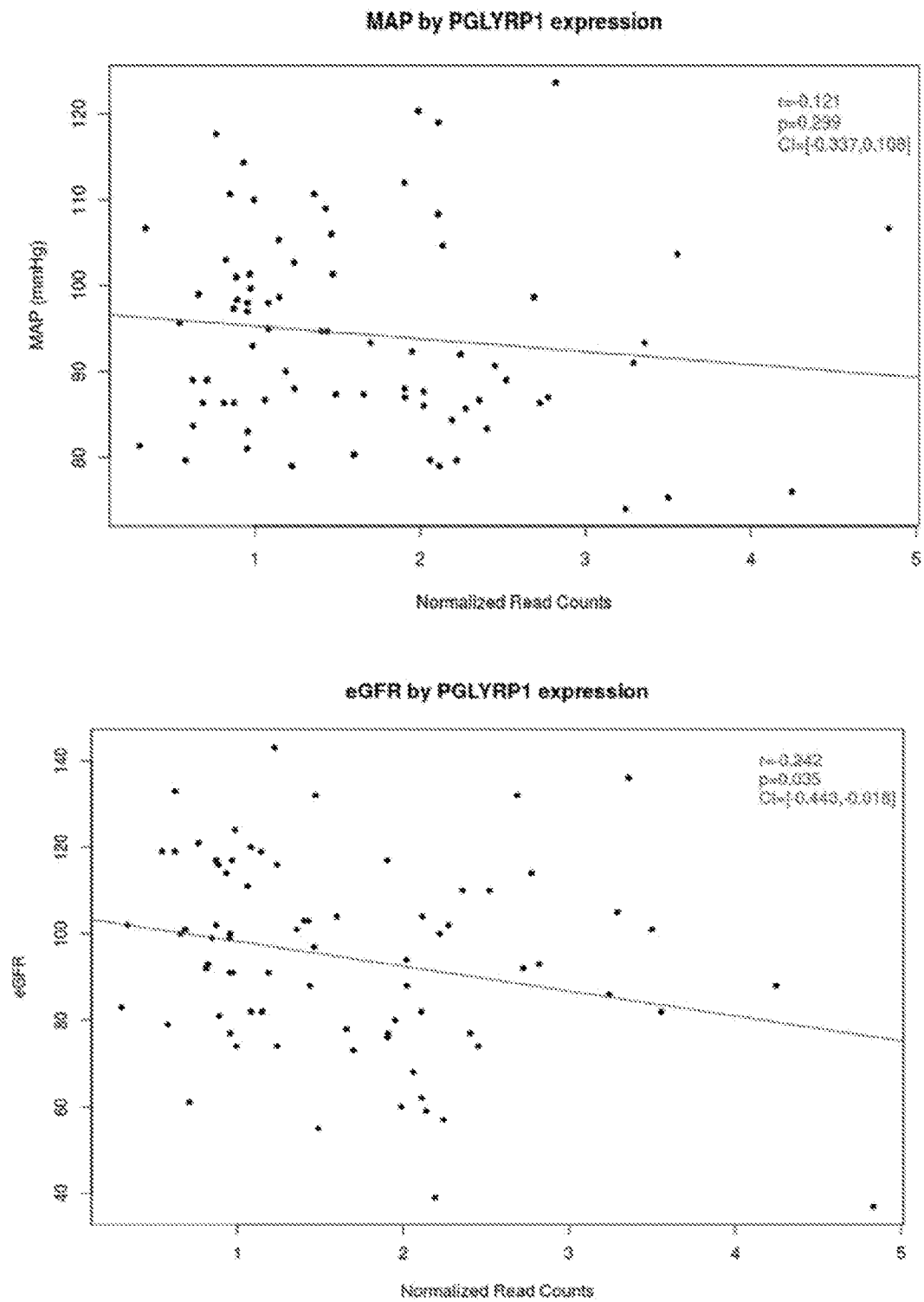


FIG. 8

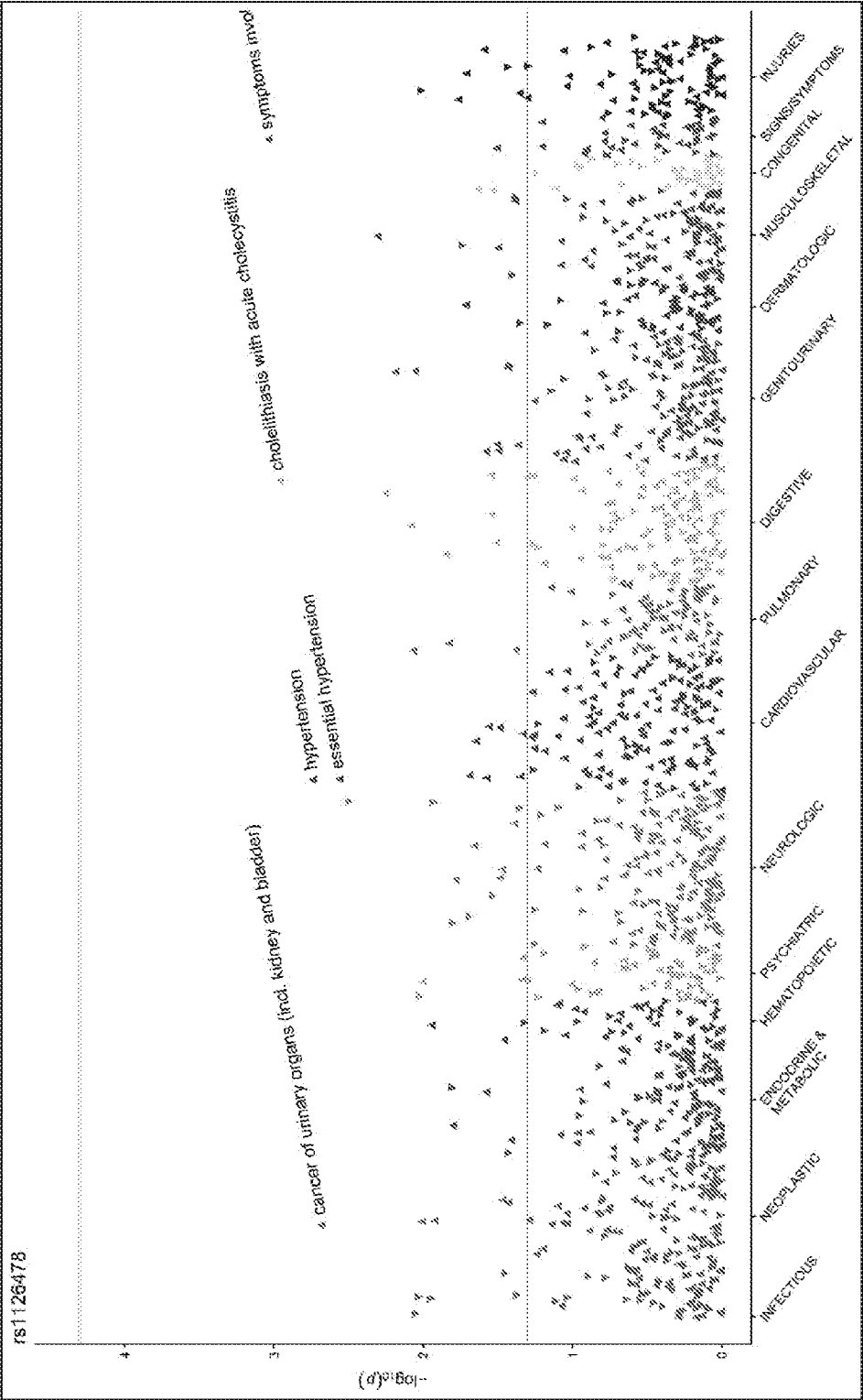


FIG. 9

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 18/29482

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12Q 1/68, G01N 33/48, G01N 33/53 (2018.01)

CPC - C12Q 2600/118, G01N 33/53, G01N 2800/50, G01N 2800/52, C12Q 1/68, C12Q 2600/158, C12Q 1/6876, G01N 33/48, G01N 2800/32

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

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

See Search History Document

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

See Search History Document

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category*      | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                           | Relevant to claim No.                                                                                                                                 |
|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| X<br>----<br>Y | US 2002/0155113 A1 (CHUN et al.) 24 Oct. 2002 (24.10.2002) para [0012], [0023], [0083], [0089], [0099], [0100], [0101], [0103 - 0104], [0107 - 0109], [0116], [0122], [0124], [0217], [0221], [0172], [0316], [0219], [0269], [0287], [0302], [0316 - 0317]. | 1, 4/1, 5, 8/5, 12, 15/12, 16, 19, 22/19, 36-37, 40-41<br>-----<br>2-3, 4/(2-3), 6, 7, 8/(6-7), 9-11, 13-14, 15/(13-14), 17-18, 20-21, 22/(20-21), 38 |
| X<br>----<br>Y | US 2010/0204058 A1 (CHANG et al.) 12 Aug. 2010 (12.08.2010), para [0013], [0116], [0018], [0049], [0051], [0115 - 0116], [0131], and Claim 11.                                                                                                               | 39<br>-----<br>2-3, 4/(2-3), 6, 7, 8/(6-7), 9-11, 13-14, 15/(13-14), 17-18, 20-21, 22/(20-21), 38                                                     |

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

☐ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

6 July 2018

Date of mailing of the international search report

01 AUG 2018

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents  
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300  
PCT OSP: 571-272-7774

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/29482

## Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

- a. ☐ forming part of the international application as filed:
  - ☐ in the form of an Annex C/ST.25 text file.
  - ☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13ter. 1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
  - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter. 1(a)).
  - ☐ on paper or in the form of an image file (Rule 13ter. 1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

The electronic sequence listing submitted on 08 June 2018 in response to the PCT/ISA/225 issued on 10 May 2018 is acknowledged; however, no required late furnishing fee as set forth in 37 CFR 1.445(a)(5) was not provided. Therefore, the international search was not carried out on the basis of that non-compliant electronic sequence listing.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/29482

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

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

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☒ Claims Nos.: 23-35  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.