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(54) **POLYPHENOL BLEND OF CURCUMIN EXTRACT AND POMEGRANATE EXTRACT AND METHODS OF IMPROVING IMMUNE RESPONSE**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

This invention is directed to compositions comprising curcumin extract and pomegranate extract, and methods of improving immune response with the compositions. The compositions may be administered as a prebiotic and/or a dietary supplement.

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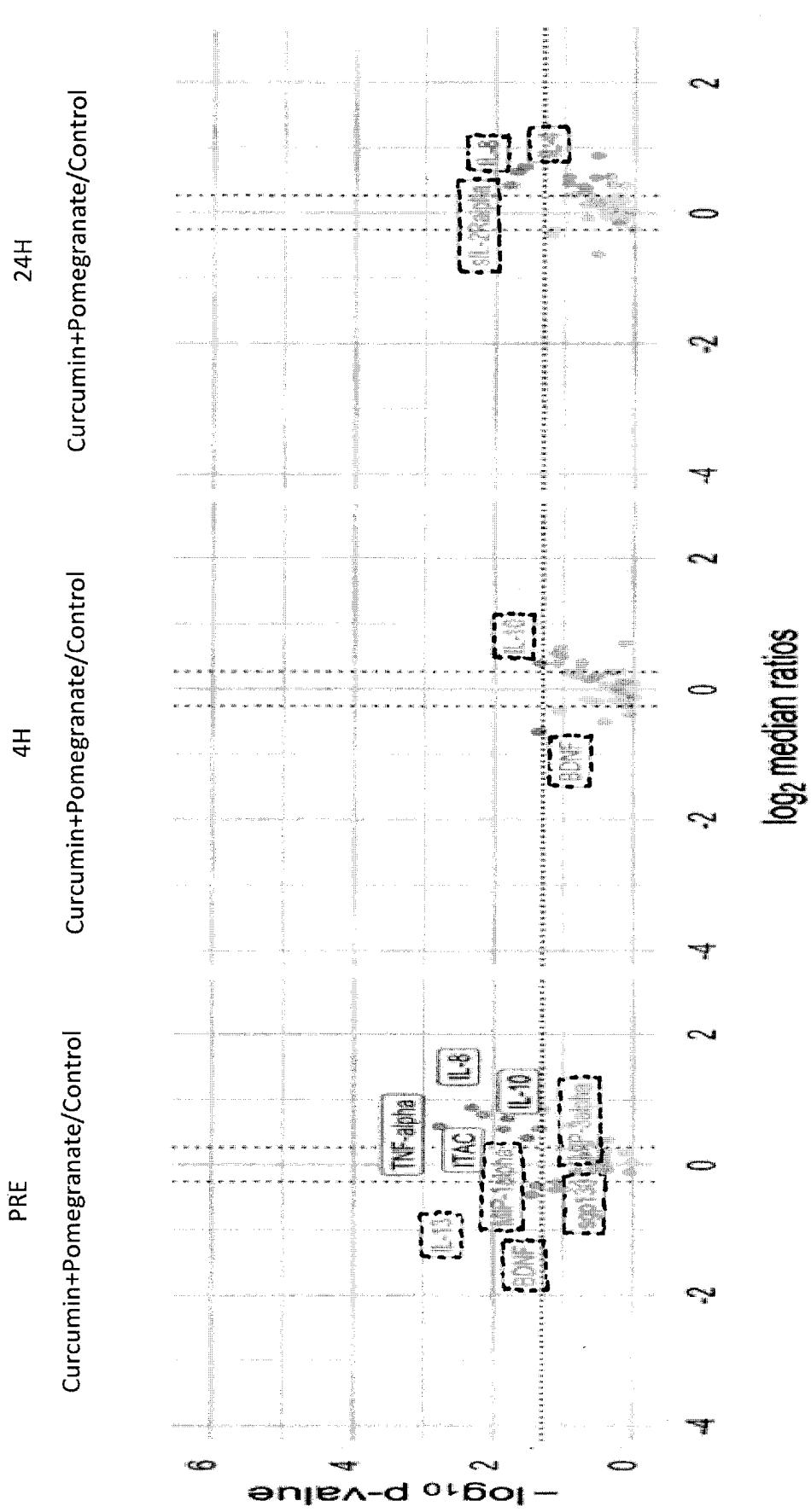


FIG. 1

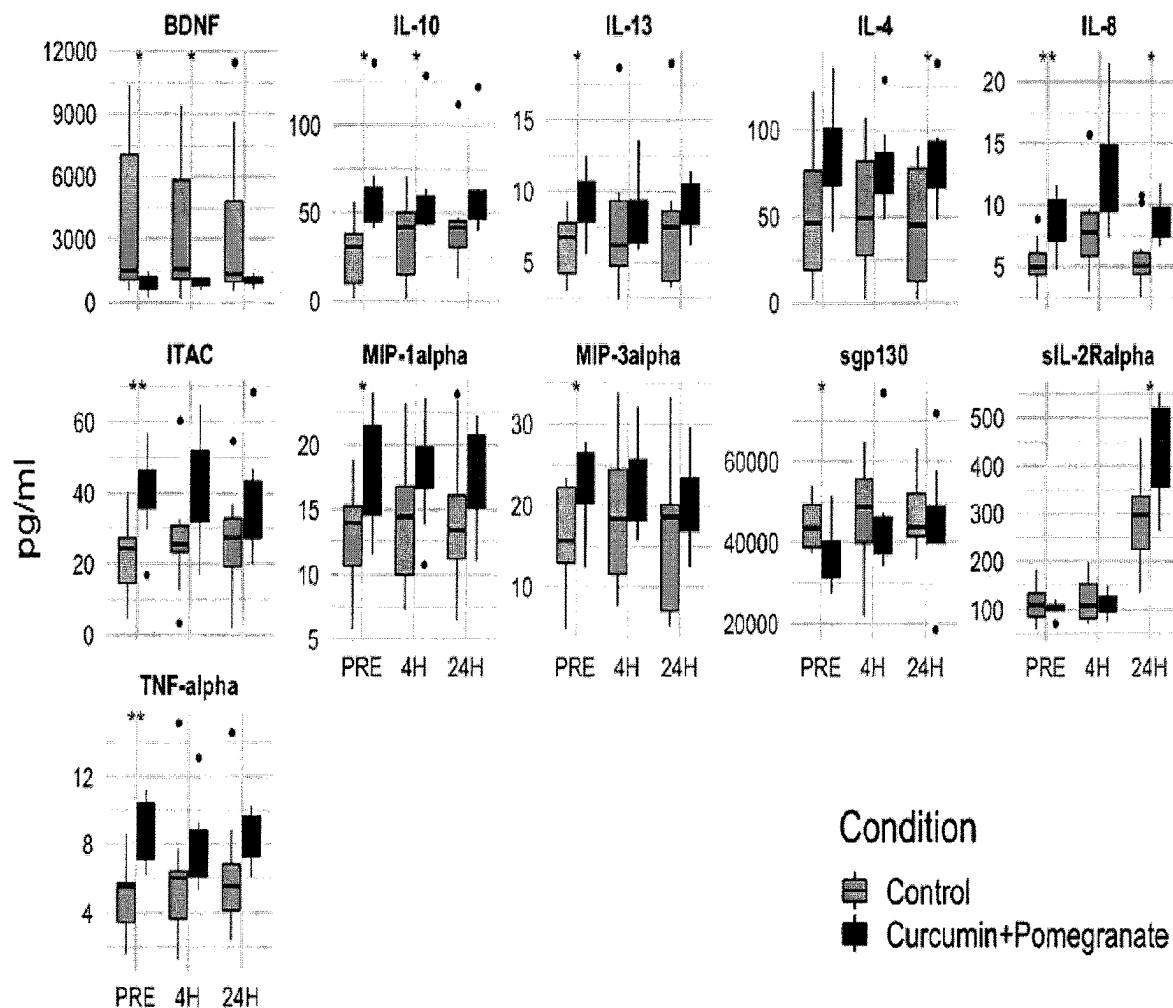


FIG. 2

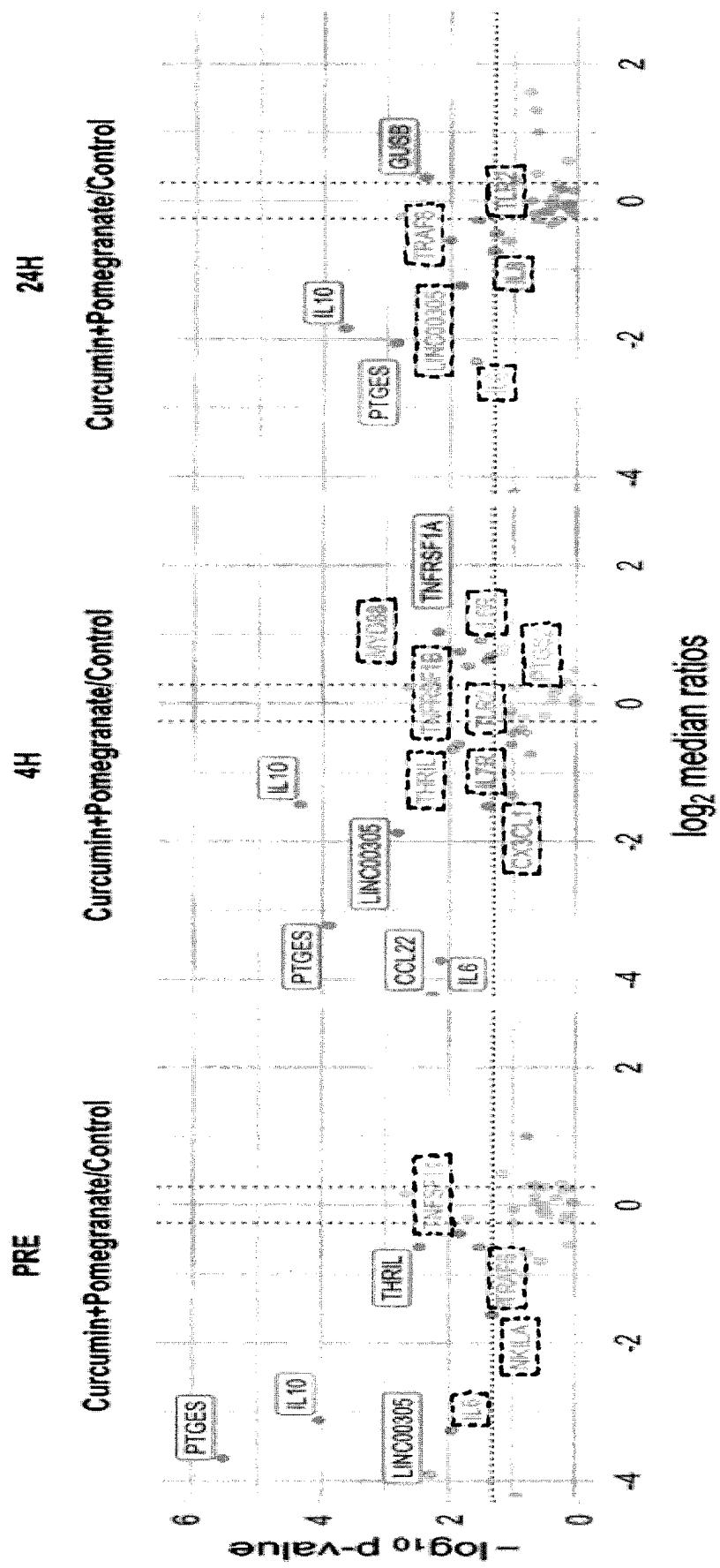


FIG. 3

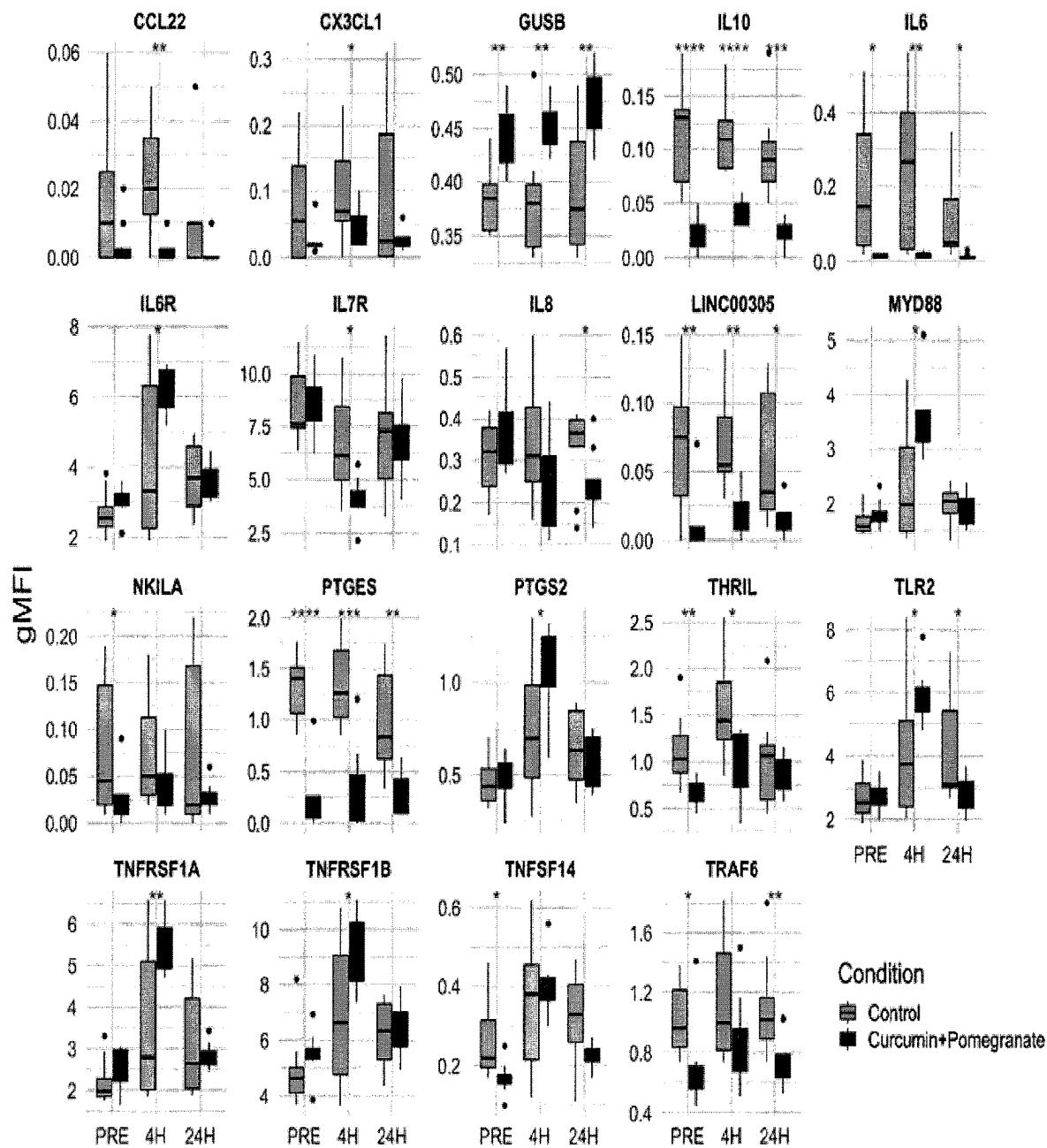


FIG. 4

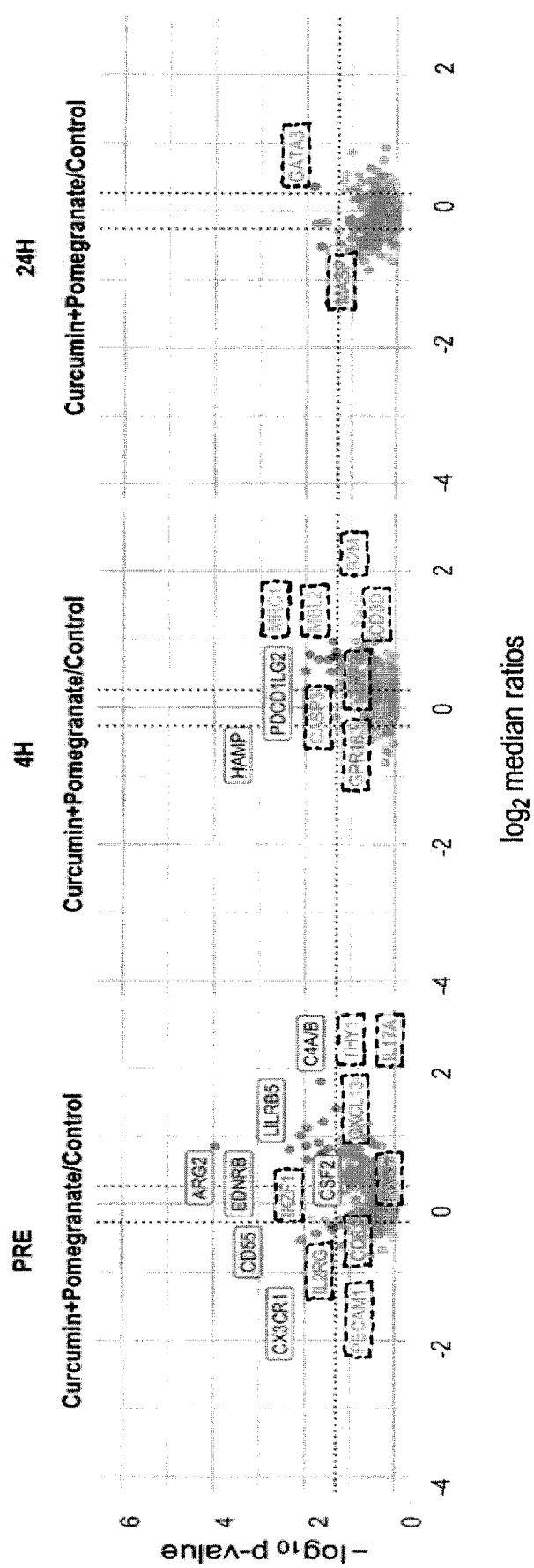


FIG. 5

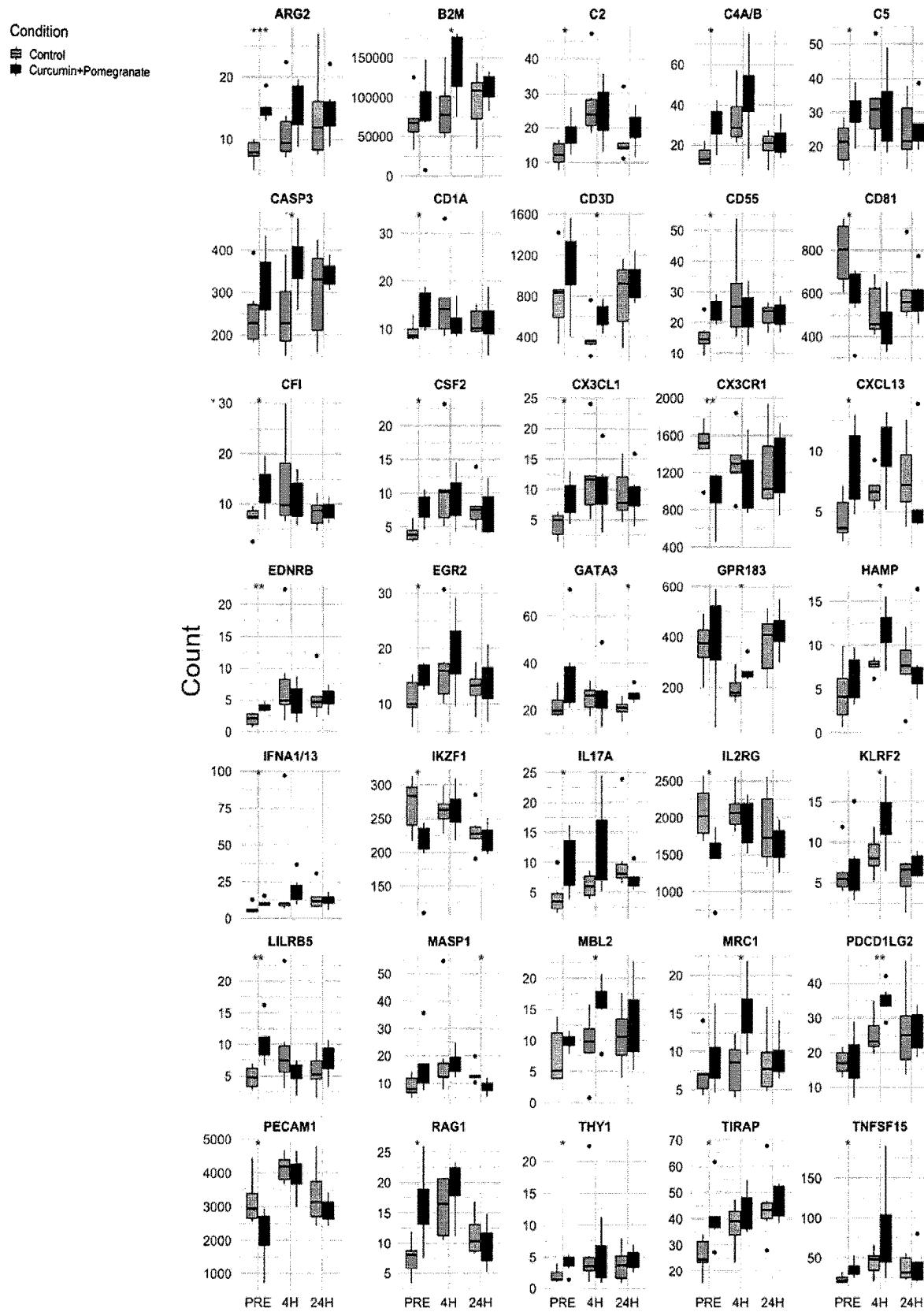


FIG. 6

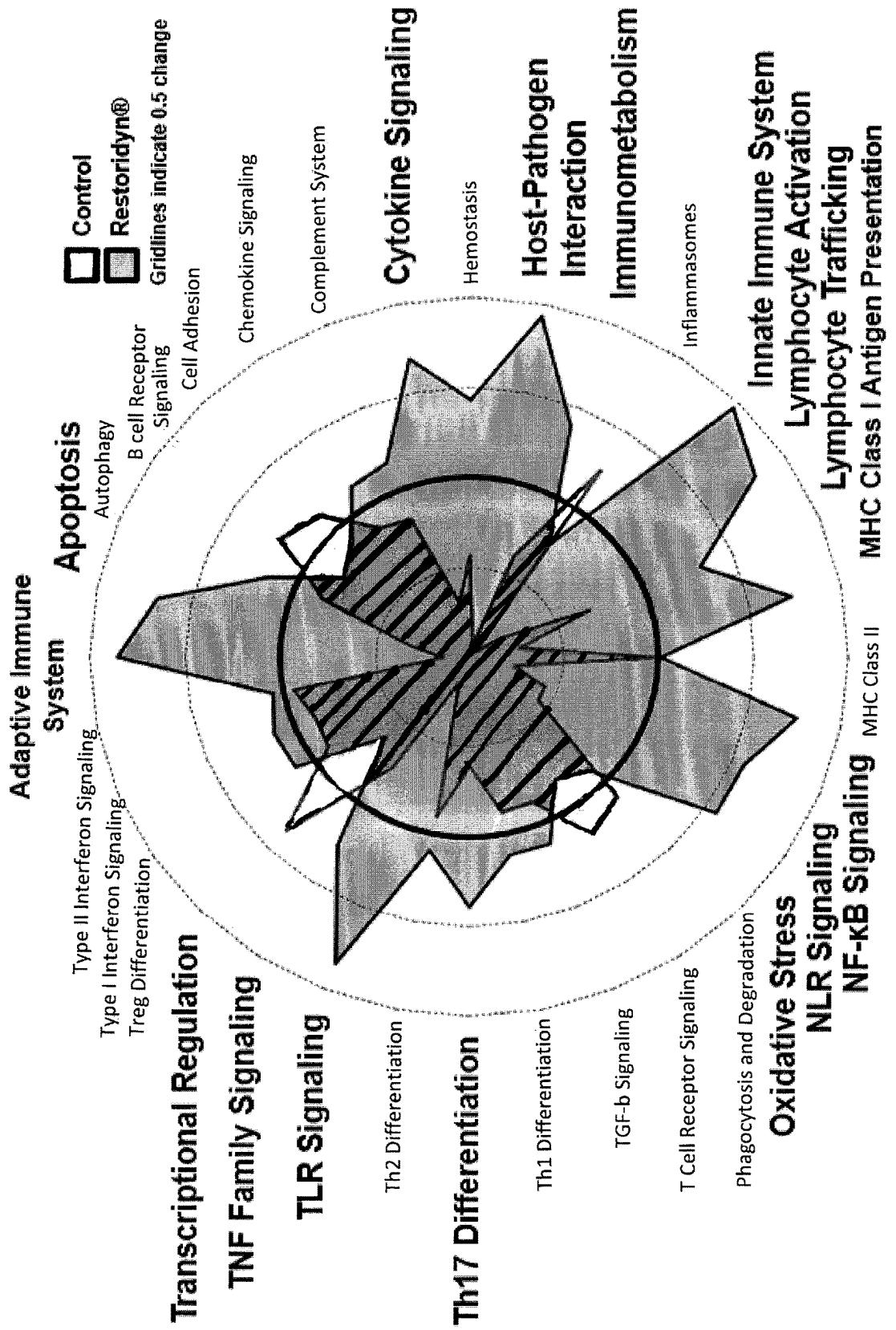


FIG. 7

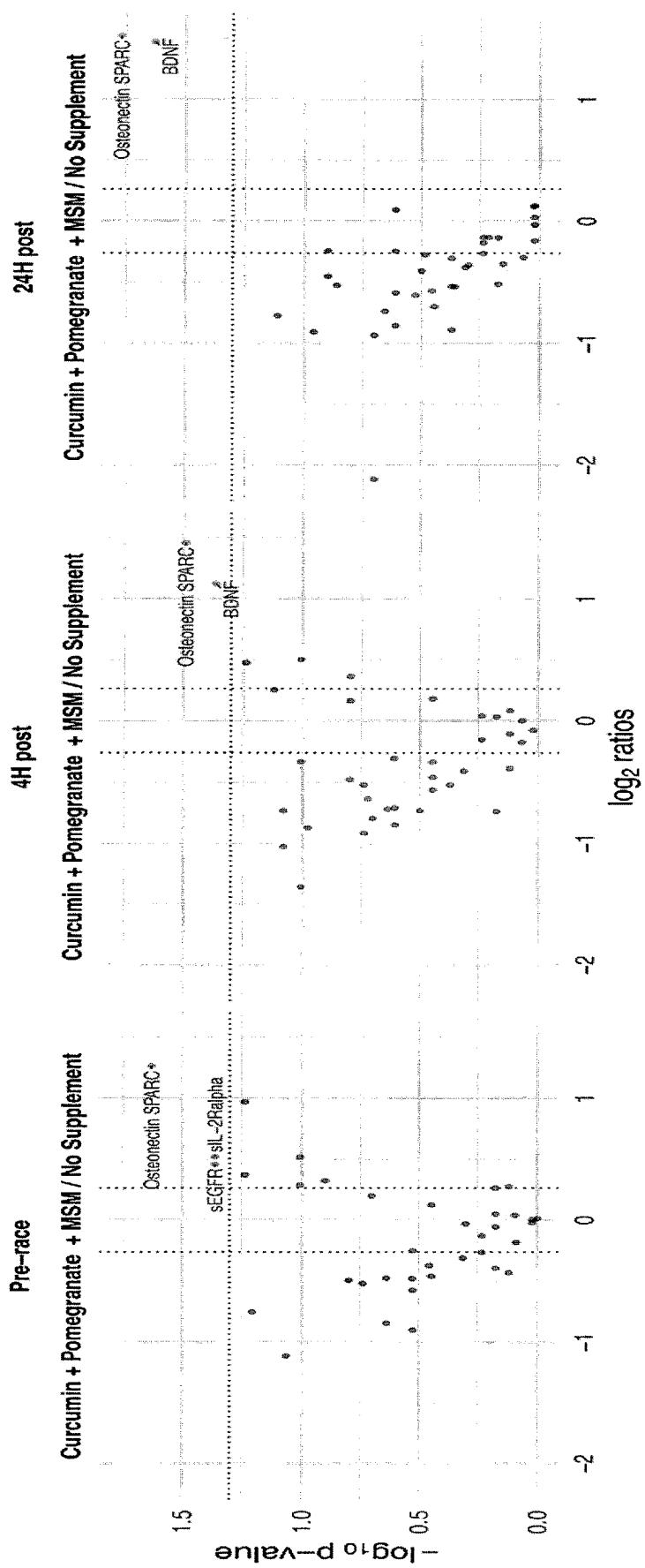


FIG. 8

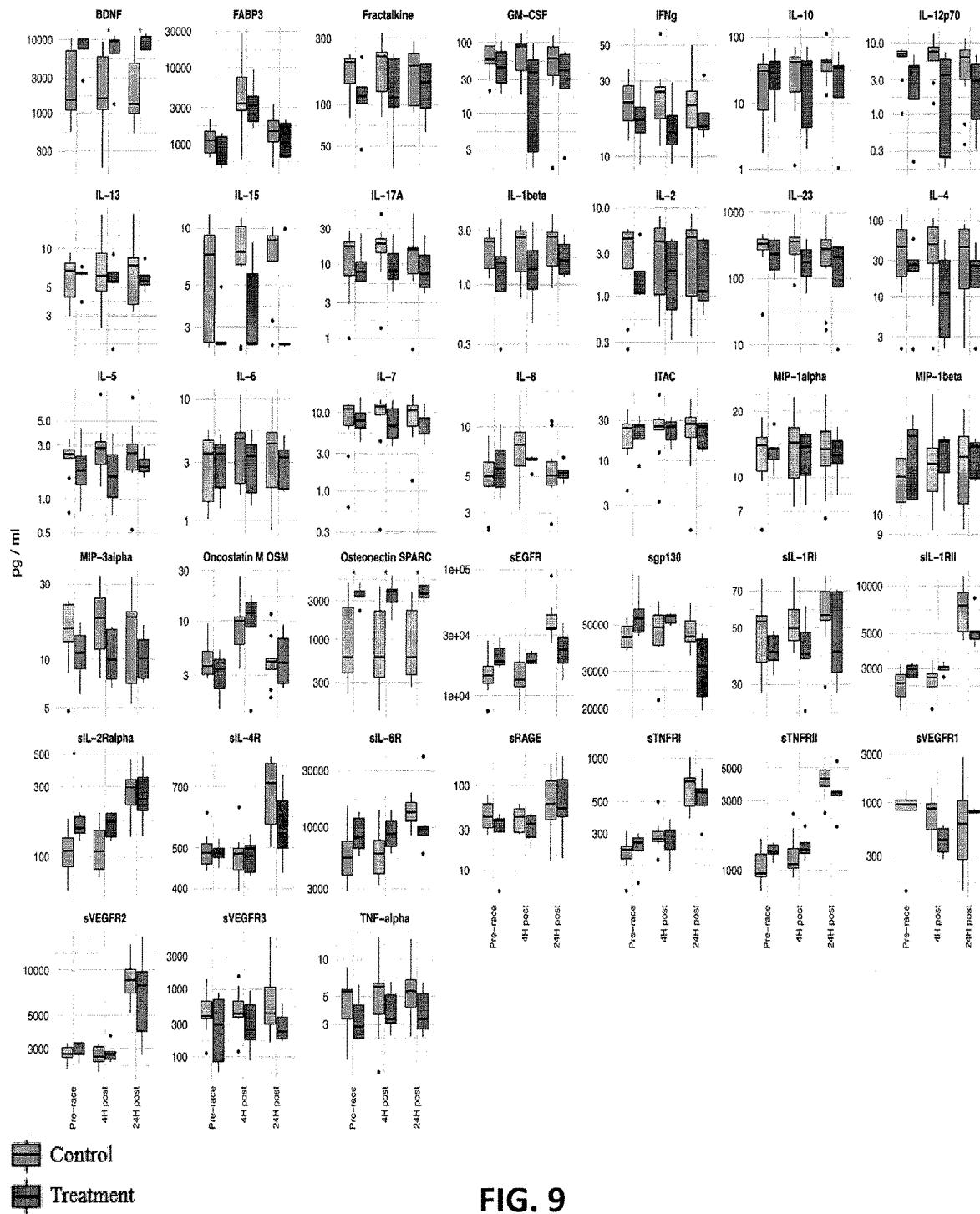
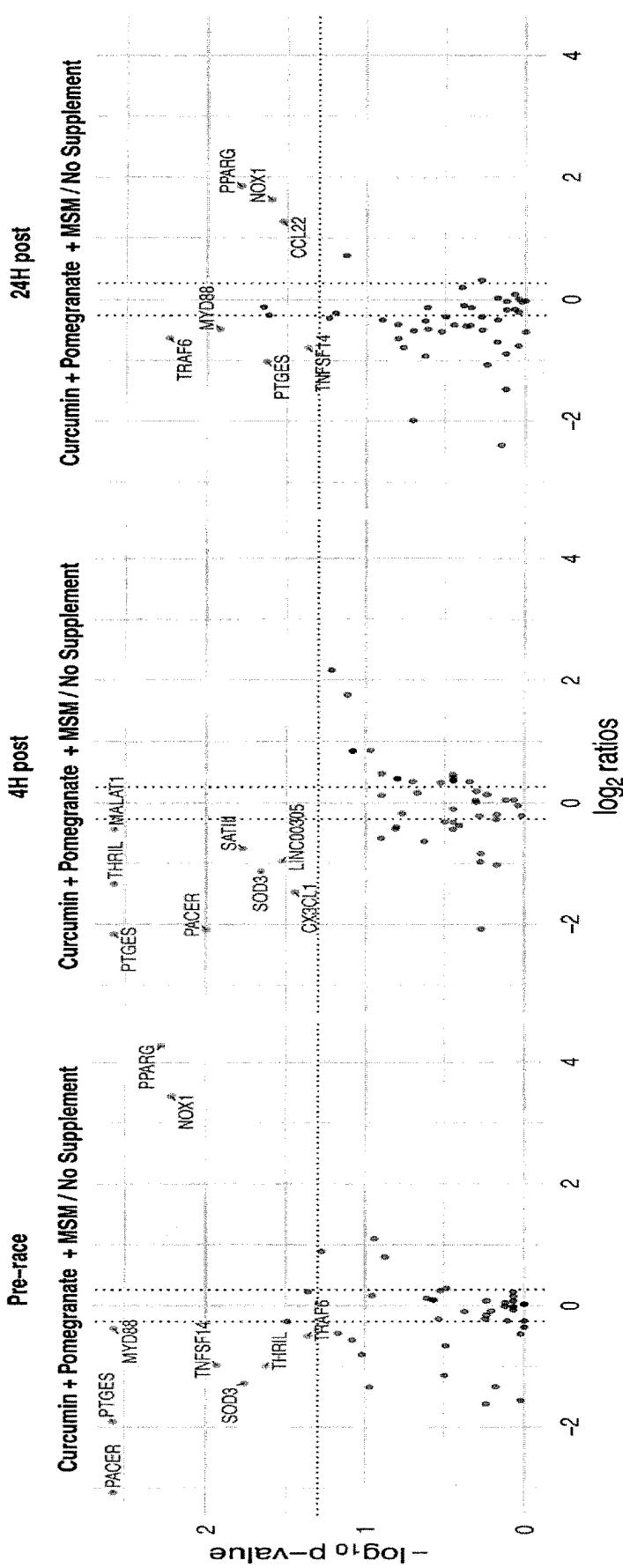


FIG. 9

**FIG. 10**

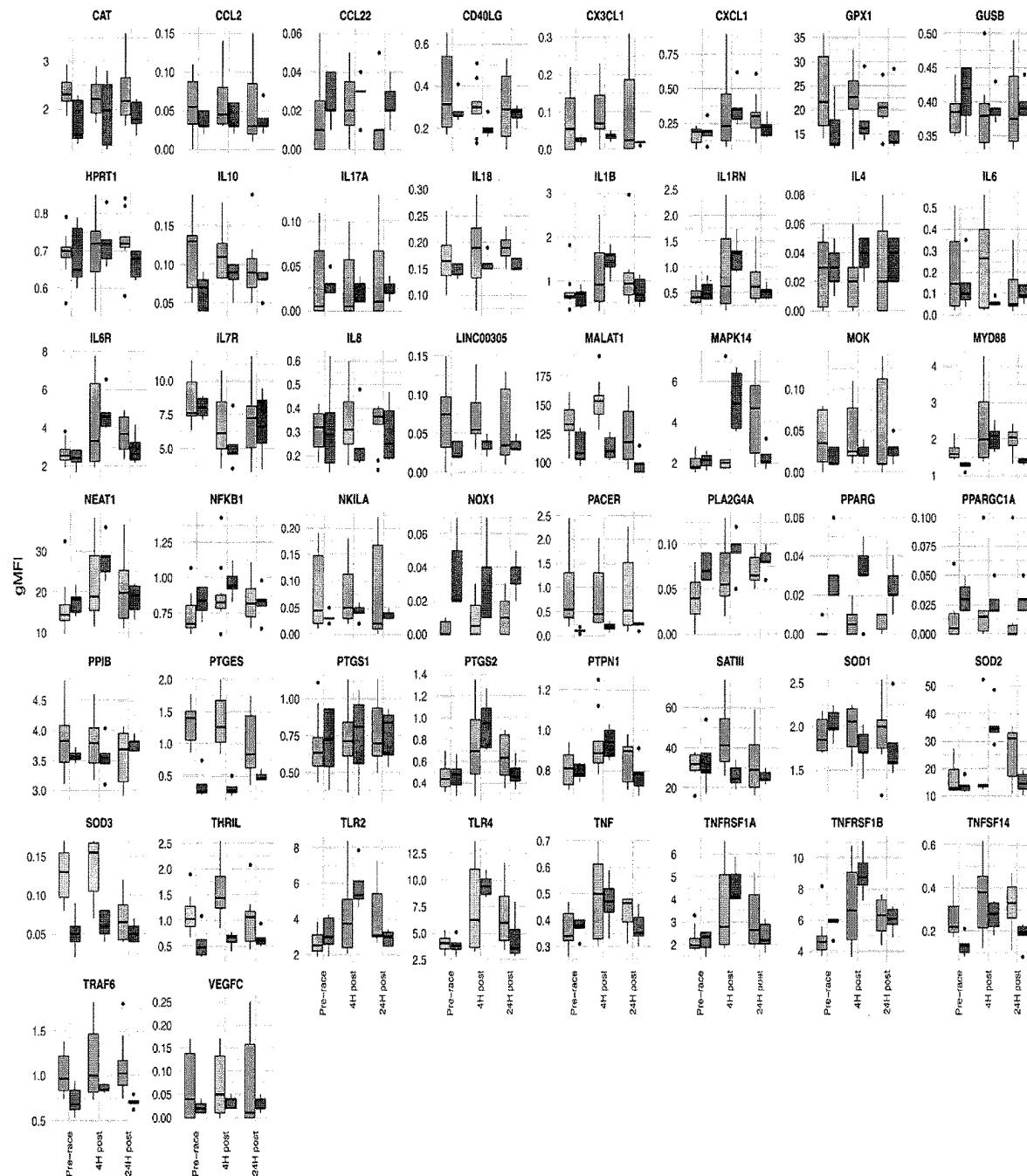


FIG. 11

1

**POLYPHENOL BLEND OF CURCUMIN
EXTRACT AND POMEGRANATE EXTRACT
AND METHODS OF IMPROVING IMMUNE
RESPONSE**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application claims priority from U.S. Provisional Application No. 63/000,263, filed Mar. 26, 2020, which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to compositions comprising curcumin and pomegranate extracts, and methods of improving immune response. The compositions may be administered as a prebiotic and/or a dietary supplement.

BACKGROUND

Maintaining a physically active lifestyle is important to overall health and wellness. Endurance running training can lead to the gradual accumulation of inflammation and soreness ultimately resulting in overuse injuries. Management of soreness and inflammation with pharmaceuticals (e.g. NSAIDs) during a long-term training regime is not a suitable solution due to known side effects (e.g. liver damage).

Curcumin (diferuloylmethane), extracted from ground rhizomes of the turmeric plant (*Curcuma longa* L. plant), is a yellow-colored, lipophilic, water-insoluble, low molecular weight polyphenol. Curcumin acts as an antioxidant and anti-inflammatory agent by enhancing activities of endogenous antioxidants (i.e. superoxide dismutase, catalase, glutathione peroxidase), blunting the action of cyclooxygenase-2 (COX-2), and blocking the activation of nuclear factor kappa beta (NF- κ b). The delivery system Longvida®, formulating curcumin with SLCP (Solid Lipid Curcumin Particle) technology, improves the bioavailability of curcumin, delivering curcumin to blood and tissues and even allowing curcumin to cross the blood-brain-barrier. U.S. Pat. No. 9,192,644 and European Patent No. 1993 365 further describe Longvida®. The improved effects are thought to be due, at least in part, to an exponential increase in bioavailability and water solubility of curcumin formulated with the SLCP technology as opposed to regular unformulated curcumin. See Nahar et al., "Anti-Inflammatory Effects of Novel Standardized Solid Lipid Curcumin Formulations" *J. Med. Food* 18(7):786-792 (2015), showing up to a 760,000-fold increase in water solubility of curcumin when formulated with SLCP technology (Nahar Table 1).

Pomegranates (*Punica granatum*) are rich in polyphenolic compounds such as ellagitannins, including characteristic punicalagins and punicalins. Ellagitannins are hydrolysable tannins having antioxidant activity. [Liu et al., "Liquid Chromatography Coupled with Time-of-flight Tandem Mass Spectrometry for Comprehensive Phenolic Characterization of Pomegranate Fruit and Flower Extracts Used as Ingredients in Botanical Dietary Supplements" *J. Sep. Sci.* 41(15): 3022-33 (2018)], U.S. Pat. Nos. 7,638,640; 7,897,791; and 7,919,636 describe some pomegranate extracts. Punicalagins and other components of pomegranate extracts may be metabolized in the gut to urolithins. Pomegranate and methylsulfonylmethane (MSM) have been shown to reduce oxidative stress and improve markers of systemic inflammation through downregulation of COX-2, NF- κ b, and tumor necrosis factor alpha (TNF α). Pomegranate fruit

2

extract has been shown to suppress high-fat diet-induced hepatic and neurological disease. [Pfohl et al. "Hepatoprotective and Anti-Inflammatory Effects of a Standardized Pomegranate (*Punica granatum*) Fruit Extract in High Fat Diet-Induced Obese C57BL/6 Mice" *Int. J. Food Sci. Nutr.* 1-12 (2020)].

A composition that supports or improves the immune system, under everyday circumstances or for instance after strenuous exercise, would be beneficial.

SUMMARY OF THE INVENTION

The present invention is directed to compositions comprising a combination of a curcumin extract and a pomegranate extract, and their use in methods for supporting and/or improving immune health, supporting and/or improving gut health, reducing feelings of stress and/or effects of stress, reducing risk of infection, and/or treating and/or preventing diseases and/or disorders of the immune system.

The present invention is directed to a composition comprising a combination of a curcumin extract and a pomegranate extract; in an embodiment, a synergistic composition and/or combination providing a synergistic effect. In an embodiment, the composition and/or combination comprises 5-30% by weight curcuminoids and 3-50% by weight punicalagins; in an embodiment, said composition and/or combination comprises not less than 10% w/w total curcuminoids, not less than 5% w/w punicalagins, and 20-30% w/w total pomegranate polyphenols. In an embodiment, the combination is a ratio of curcumin extract:pomegranate extract in the range of about 5:1 to about 1:5 (w/w). In an embodiment, the above embodiments or other specific compositions of this invention are synergistic. In an embodiment, the curcumin extract is an optimized curcumin extract, in an embodiment Longvida®. In an embodiment, the pomegranate extract is the proprietary pomegranate extract, Pomella®.

The present invention is also directed to a method of supporting and/or improving immune health in a subject, including a healthy subject or a subject having an infection, comprising the steps of providing a composition comprising an effective amount of a combination of a curcumin extract, such as an optimized curcumin extract, and a pomegranate extract, and administering the composition to a subject in need thereof to support the immune system of the subject, such as the innate immune system and/or the adaptive immune system. In an embodiment, the method and combination of extracts of this invention are synergistic and/or provide significant results.

The present invention is also directed to a method of treating and/or preventing an immune-related disease or disorder in a subject, and/or treating or preventing a symptom thereof, comprising the steps of providing a composition comprising an effective amount of a combination of a curcumin extract and a pomegranate extract, in an embodiment in the range of about 5:1 to about 1:5 (w/w), in an embodiment where the curcumin extract is an optimized curcumin extract, in an embodiment Longvida®, and said pomegranate extract is Pomella®; and then administering the composition to the subject. In an embodiment, the method and combination of extracts are synergistic and/or provide significant results. In an embodiment, the disease treated is a viral or bacterial or other infection, such as COVID 19, a viral infection, or such as bronchitis, a bacterial or viral infection.

The present invention is also directed to a method of supporting and/or improving gut health in a subject, comprising the steps of providing a composition comprising an

effective amount of a combination of a curcumin extract and a pomegranate extract, and then orally administering the composition to a subject in need thereof. In an embodiment, the method and combination of extracts are synergistic and/or provide significant results.

The present invention is also directed to a method of reducing feelings of stress or effects of stress in a subject, comprising the steps of providing a composition comprising an effective amount of a combination of a curcumin extract and a pomegranate extract, and administering the composition to a subject in need thereof. In an embodiment, the method and combination of extracts are synergistic and/or provide significant results.

The present invention is also directed to a method of reducing infection risk in a subject, comprising the steps of providing a composition comprising an effective amount of a combination of a curcumin extract and a pomegranate extract, and then administering the composition to a subject in need thereof. In an embodiment, the method and combination of extracts are synergistic and/or provide significant results.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a volcano plot showing protein biomarkers for inflammation that significantly increased or decreased in subjects administered a composition having curcumin extract and pomegranate extract of the present invention, compared with control, before running a half-marathon (PRE), 4 hours after completion of the half-marathon (4 H), and 24 hours after completion of the half-marathon (24 H).

FIG. 2 shows concentrations of protein biomarkers for inflammation that significantly increased or decreased in subjects administered a composition having curcumin extract and pomegranate extract of the present invention, compared with control, before running a half-marathon (PRE), 4 hours after completion of the half-marathon (4 H), and 24 hours after completion of the half-marathon (24 H).

FIG. 3 shows a volcano plot showing RNA relating to inflammation that significantly increased or decreased in subjects administered a composition having curcumin extract and pomegranate extract of the present invention, compared with control, before running a half-marathon (PRE), 4 hours after completion of the half-marathon (4 H), and 24 hours after completion of the half-marathon (24 H).

FIG. 4 shows concentrations of RNA relating to inflammation that significantly increased or decreased in subjects administered a composition having curcumin extract and pomegranate extract of the present invention, compared with control, before running a half-marathon (PRE), 4 hours after completion of the half-marathon (4 H), and 24 hours after completion of the half-marathon (24 H).

FIG. 5 shows a volcano plot showing significant upregulation or downregulation of mRNA expression in markers of immune response in subjects administered a composition having curcumin extract and pomegranate extract of the present invention, compared with control, before running a half-marathon (PRE), 4 hours after completion of the half-marathon (4 H), and 24 hours after completion of the half-marathon (24 H).

FIG. 6 shows concentrations of mRNA in markers of immune response in subjects administered a composition having curcumin extract and pomegranate extract of the present invention, compared with control, before running a half-marathon (PRE), 4 hours after completion of the half-marathon (4 H), and 24 hours after completion of the half-marathon (24 H).

FIG. 7 illustrates immune system changes in subjects administered a composition having curcumin extract and pomegranate extract of the present invention, compared with control, after running a half-marathon. Control (white), 5 Restoridyn® (shaded), overlap (striped).

FIG. 8 is a volcano plot showing protein biomarkers significantly upregulated before running a half-marathon (PRE), 4 hours after completion of the half-marathon (4 H), and 24 hours after completion of the half-marathon (24 H).

10 FIG. 9 shows concentrations of protein biomarkers (pg/ml) significantly upregulated before running a half-marathon (PRE), 4 hours after completion of the half-marathon (4 H), and 24 hours after completion of the half-marathon (24 H).

15 FIG. 10 is a volcano plot showing RNA biomarkers significantly upregulated before running a half-marathon (PRE), 4 hours after completion of the half-marathon (4 H), and 24 hours after completion of the half-marathon (24 H).

20 FIG. 11 shows numerical changes for all RNA measured (gMFI; geometric mean of median fluorescent intensity) before running a half-marathon (PRE), 4 hours after completion of the half-marathon (4 H), and 24 hours after completion of the half-marathon (24 H).

DETAILED DESCRIPTION

The present invention is directed to a composition comprising a curcumin extract and a pomegranate extract. The extracts, taken together, synergistically support and/or improve immune health, support and/or improve gut health, reduce feelings of stress and/or effects of stress, reduce risk of infection, and/or treat and/or prevent diseases and/or disorders of the immune system. Methods of using a combination of a curcumin extract and a pomegranate extract of the present invention also improve immune health, support and/or improve gut health, reduce feelings of stress and/or effects of stress, reduce risk of infection, and/or treat and/or prevent diseases and/or disorders of the immune system. A composition of the present invention may also include components and/or metabolites of curcumin extract and pomegranate extract. Isolated, purified, and/or synthetic curcuminooids, punicalagins, punicalins, urolithins, and other components of their metabolic pathway as available may be added to a composition of the present invention, or added in place of another component. Methylsulfonylmethane may be included in a composition of the present invention, or may be omitted.

In an embodiment, a composition of the present invention reduces the risk of infection and/or injury and promotes recovery from exercise-induced infection or injury, such as from strenuous exercise such as a half-marathon or training for a half-marathon, by increasing, modulating, and/or strengthening a subject's immune response, for instance in response to a cytokine storm. Over time, repeated exercise and physical training can increase the time needed for bodily tissues to recover. When that time is not taken, minor injuries can lead to major injuries, particularly during an exercise event. Administration of a composition of the present invention stimulates the immune response to reduce infection risk during times of stress and minor injury in the body, reducing the risk for further infection or injury, and reducing the risk for major infection or injury. Common ailments associated with endurance athletes in heavy training is their susceptibility to virus and bacterial infections such as bronchitis and flu (lung inflammation). Administration of compositions of the present invention afforded 15% more training sessions, 10% greater training volume, 6%

improvement in Post-Half Marathon 10 k time trials. In an embodiment, infection and injury risk is reduced and recovery is promoted by the administration of the present compositions, without strenuous exercise, via the administration of a composition of this invention.

The present invention is also directed to a method of immunomodulating the immune system such as its pathways in a subject, comprising the steps of providing a composition of this invention and administering an effective amount to a subject to reach the blood stream and bodily tissues and cells of the subject, and up regulate or down regulate mRNA expression related to immune pathways including Th17 Differentiation pathway, Toll-like receptor signaling pathway, Cytokine Signaling pathway, NF- κ B Signaling pathway, NLR Signaling pathway, T cell receptor signaling pathway/Lymphocyte Activation pathway, TNF Family Signaling, in the subject. In an embodiment, administration according to this method is oral. The present invention is also directed to a method of immunomodulating immune system pathways in a subject via up regulation or down regulation of protein expression related to immune response, in a subject, comprising the steps of providing a composition comprising an effective amount of a combination of a curcumin extract and a pomegranate extract, and then orally administering the composition to a subject in need thereof, to immunomodulate the subject's immune system. Immunomodulating the immune system promotes immune health in a subject, restoring a balanced immune response to those in need, or maintaining balance, for instance allowing proinflammation in areas of healing while minimizing/modulating responses such as a cytokine storm response, and thus avoiding additional immune weaknesses, and strengthening the immune response and overall immune health of the subject. Immunomodulation may for instance promote immune health in a subject, adjust the immune system and its responses and/or help it self-regulate as needed by the subject.

The below definitions and discussion are intended to guide understanding but are not intended to be limiting with regard to other disclosures in this application. References to percentage (%) and ratios in compositions of the present invention refers to the % by weight of a given component to the total weight of the composition being discussed or ratios of the weight of specified substances, also signified by "w/w" or "wt/wt", unless stated otherwise.

A "curcumin extract" according to the present invention is an extract of turmeric root containing curcumin (diferuloylmethane). In an embodiment, a curcumin extract of the present invention includes at least 1-100% curcumin (wt/wt); 2-95% curcumin (wt/wt); 10-95% curcumin (wt/wt); 20-95% curcumin (wt/wt); 40-50% curcumin (wt/wt); 50-60% curcumin (wt/wt); 60-70% curcumin (wt/wt); 70-80% curcumin (wt/wt) including for instance 75-78% curcumin (wt/wt); 80-97% curcumin (wt/wt); 90-100% curcumin (wt/wt), including for instance 93-97% curcumin (wt/wt); 95% curcumin (wt/wt). A curcumin extract may include a variety of curcuminoids, including for instance curcumin, tetrahydrocurcumin, demethoxycurcumin, bisdemethoxycurcumin, curcumin esters (which may function as prodrugs), and mixtures thereof. In an embodiment, a composition of the present invention may include a combination of curcumin and a metabolite of curcumin, tetrahydrocurcumin. In an embodiment, the curcumin extract is standardized. In an embodiment, a curcumin extract of this invention is in solid form such as a powder, or in a liquid or

semi-liquid form. See for instance Tables 1 and 2 for examples of a curcumin extract used in the present invention.

According to an embodiment of this invention, a curcumin extract is formulated and delivered to the bloodstream and tissues of the body by a delivery system such as solid lipid curcumin particle (SLCP) technology. In an embodiment, curcumin optimized for delivery by SLCP technology is Longvida®. In an embodiment, curcumin optimized for delivery, by SLCP or another technology, is not Longvida®. Optimized curcumin according to the present invention delivers non-glucuronidated curcumin (and in an embodiment non-sulfated curcumin) to the tissues and blood of the body, including for instance via lymphatic transport and by allowing the curcumin to cross the blood-brain-barrier. [See for instance Eidenberger et al., "*Investigation of the Lymphatic Transport of Solid-Lipid Curcumin Particles (Longvida®) in Comparison to Curcumin Extract in Rats*" in 252nd ACS National Meeting, Philadelphia, Pa.: 55 (2016)]. U.S. Pat. No. 9,192,644 is incorporated by reference into this application for the purpose of describing optimized curcumin and its preparation.

For instance, optimized curcumin may be prepared with mole fractions of stearic acid (0.710), lecithin (0.210), taurocholate (0.069), curcumin (0.011), with surfactants stirred into 75° C. water and then the water-surfactant solution added to the melted lipid at 75° C. and then homogenized into an emulsion, typically 18,000 to 30,000 rpm for 70-150 seconds. The dispersed lipid phase of the emulsion is solidified by dispersing 1 mL emulsion aliquots through a narrow gauge needle into near ice cold water (about 2° C.), at a ratio of 1:20 warm micro-emulsion:cold water, to produce solid lipid nanoparticles. The solid lipid nanoparticles are washed three times with distilled water and sterilized and stored sterile at 4° C.

Solid Lipid Nanoparticles (SLN) Preparation Starting Formula.

Stearic Acid mole fraction 0.710; lecithin mole fraction 0.210; taurocholate mole fraction 0.069; curcumin or other curcuminoid varies stepwise around mole fraction 0.011. Stearic acid lipid is maintained at ~75° C. to melt completely. Separately, double distilled water is heated to 75° C. Typically, surfactants are added to the water under magnetic stirring and allowed to equilibrate at 75° C. The water-surfactant solution is added to the melted lipid and allowed to equilibrate at 75° C. The IKA Ultra-Turrax T 18 rotor-stator homogenizer is then used to achieve adequate mixing, typically 18,000-30,000 rpm for 70-150 sec. Once mixed, the dispersed lipid phase of the emulsion is solidified in order to produce the solid lipid nanoparticles by dispersing through a narrow gauge needle 1 ml emulsion aliquots into continuously stirred near ice cold water (~2° C.) at a ratio of 1:20 (warm micro-emulsion:cold water). The final product is washed three times with distilled water and filter sterilized with an Amicon Diaflo apparatus with YM100 membranes (cut off 100 000 Dalton) and stored sterile at 4° C. until delivery by gavage. Multiple lipid nanoparticle samples can be prepared from one micro-emulsion batch.

In an embodiment, optimized curcumin may be administered orally. Optimized curcumin has improved oral bioavailability over regular curcumin. In an embodiment, optimized curcumin may be administered parenterally. Optimized curcumin for parenteral administration may be particles sized approximately 100 nm, for instance in the range of 50-150 nm; for oral administration, optimized curcumin particles may be sized larger, for instance approxi-

mately 50-500 nm. In an embodiment, for parenteral administration, the polydispersity of optimized curcumin is about 0.10.

A “pomegranate extract” according to the present invention is prepared by extracting chemicals from a pomegranate. In an embodiment, the pomegranate extract is standardized. The pomegranate extract comprises at least 2% (w/w) punicalagins, up to 100% punicalagins. The pomegranate extract also comprises free ellagic acid. In an embodiment, the content of the free ellagic acid is such that the ratio of punicalagins:free ellagic acid (w/w) is in the range of 10:1 to 35:1. In an embodiment, the total phenol content of a pomegranate extract of the invention is at least 5% (w/w) (expressed as gallic acid equivalent). The solubility of a pomegranate extract in water is at least 3% (w/w), for instance, 30 g pomegranate extract/liter. In an embodiment, the pomegranate extract contains minimal or no traces of organic solvents such as methanol, ethanol, isopropanol, which are commonly employed in purification steps to prepare a pomegranate extract. In an embodiment, said minimal or no traces of organic solvents are 1 ppb or less. An example of a pomegranate extract according to this invention is Pomella®. A formulation of proprietary pomegranate extract according to the present invention may be designed to provide high levels (e.g. at least 20%) of ellagitannins, in particular punicalagins. In an embodiment, a pomegranate extract of this invention is in solid form such as a powder, or in a liquid or semi-liquid form. See for instance Tables 1 and 2 for examples of a pomegranate extract used in the present invention.

In an embodiment, a pomegranate extract of this invention comprises at least 5% (w/w) punicalagins, for instance in the range of 5-50% (w/w) punicalagins, including for instance 30-50% (w/w) punicalagins, 35-45% (w/w) punicalagins, 40-50% (w/w) punicalagins, 40-45% (w/w) punicalagins, and other ranges as provided throughout this application; and the total phenol content is at least 10%-50% (w/w) (expressed as gallic acid equivalent), including for instance 20% or 30%, and other values within the range. The solubility of the extract in water is at least 3%, as described above, and in an embodiment, the extract has a content of residual organic solvents of 0-1 ppb.

In an embodiment, an enzyme capable of hydrolyzing punicalagins and/or punicalains to ellagic acid is used in a pomegranate extract of this invention. In an embodiment, a pomegranate extract of this invention has a ratio of punicalagins:ellagic acid (% w/w) in the range of 10:1 to 35:1. In an embodiment, a pomegranate extract of this invention includes 20-50% (w/w) ellagic acid, in an embodiment 30-45% (w/w) ellagic acid, in an embodiment, 40% (w/w) ellagic acid.

In an embodiment, a pomegranate extract of the present invention comprises polyphenolic compounds. In an embodiment, the polyphenolic compounds include or are punicalagins (PA), ellagic acid (EA), urolithins such as urolithin A (UA), or a combination thereof. In an embodiment, a composition of the present invention comprises pomegranate extract, which comprises a combination of PA and EA and optionally Urolithins, such that the extract and/or composition comprises a combination of PA and EA in amount of about 3% to about 95% by weight. In an embodiment, the combination of PA and EA is from about 10% to about 90% PA and up to 10% EA by weight. In an embodiment, the combination of EA and PA is from about 10% to about 90% EA and up to 10% PA by weight. In an embodiment, the combination of PA and EA is from about 20% to about 50% PA and about 0.5% to about 5% EA by weight.

weight. In an embodiment, the combination of EA and PA is from about 20% to about 50% EA and about 0.5% to about 5% PA by weight. In an embodiment, the combination of PA and EA is from about 10% to about 50% PA and about 2.0-3.0% EA by weight. In an embodiment, the combination of EA and PA is from about 10% to about 50% EA and about 2.0-3.0% PA by weight. In an embodiment, the combination of PA, EA, and Urolithin(s) is about 3% to about 95% by weight. Also in an embodiment, the combination of PA, EA, and Urolithin(s) is from about 10 to about 50% PA, about 0.5% to about 5% EA, and 0.5 to 20% Urolithin by weight. As urolithins such as Urolithin A are gut microbial metabolites of Pomella punicalagins, and their metabolites, urolithins may not be present in Pomella®.

A pomegranate extract according to the present invention may be prepared for instance by blending all or part of a pomegranate fruit in water or aqueous solution, and removing remaining solids. In an embodiment, after removing solids, the blended solution is poured over a resin such as a polymeric resin such as XAD-16 resin so that ellagitannins such as punicalagins and punicalains adsorb to the resin, and then are eluted from the resin for instance by methanol or ethanol, and the methanol or ethanol then removed for instance by evaporation. In an embodiment, the pH before, during, or after blending is about 1-2.5.

U.S. Pat. Nos. 7,638,640; 7,897,791; and 7,919,636 describe examples of pomegranate extracts and their preparation according to the present invention, and are each incorporated by reference herein for the purpose of describing preparation methods and products.

A “composition” according to the present invention comprises, consists essentially of, or consists of a combination of curcumin extract and pomegranate extract. In an embodiment, a combination of curcumin extract and pomegranate extract of this invention is a blend of the two extracts. In an embodiment, a composition of this invention comprises a synergistic combination of curcumin extract and pomegranate extract. Such a composition may be referred to as a synergistic composition of this invention. In an embodiment, and as needed without being bound by theory, the synergies of the bioactive compounds of the curcumin extract and pomegranate extract provide a synergistically improved immune response as compared with curcumin extract or pomegranate extract alone. In an embodiment, a composition of the present invention comprises 5-30% curcuminoids and 3-50% punicalagins.

In an embodiment, a composition of this invention is a solutions dispersible complex of (i) lipid coated curcumin or curcumin micelles, and (2) pomegranate polyphenols. In an embodiment, a pomegranate extract of this invention is soluble in water, and lipid-coated curcumin or curcumin micelles are partly soluble in water. In an embodiment, when the curcumin and pomegranate extracts are combined, for instance blended, together, the lipid coated curcumin or curcumin micelles do not change if they undergo grinding, mixing, milling, encapsulation, and/or granulation/regranulation. In an embodiment, a composition of the present invention may be prepared combining the curcumin extract and pomegranate together for instance by grinding, mixing, milling, encapsulation, and/or granulation/regranulation, for instance per known techniques. In an embodiment, the particle size of a composition of this invention may be the particle size resulting from grinding, mixing, and/or granulating curcumin and pomegranate extracts, or may be reduced for instance by further grinding. Without being

bound by theory, reducing particle size according to this invention may improve dispersion and solubility. In an embodiment, a composition and/or combination of this invention is in powdered or other solid form. In an embodiment, a composition and/or combination of this invention is in liquid or semi-liquid form.

Without being bound by theory, a blend of the two extracts into a composition of this invention appears to enhance solubility. Both curcumin and punicalagins are polyphenolic, however, the combination of polyphenols does not mean they will work together. Research has shown that many times polyphenols will cancel each other out. However, in a composition of the present invention, such as a blend of the two extracts, punicalagin and curcumin both have anti-inflammatory potential, however, it appears that when combined synergy from the combination of the extracts occurs, with actions further down the cellular pathway and mRNA's with impact on several immune system pathways, including improving those associated with responding to cytokine storm, stimulating innate immune pathways, and stimulating host-pathogen pathways, whether the immune system is impacted from stress from exercise or from pathogens.

In an embodiment, a combination of curcumin extract and pomegranate extract of the present invention comprises not less than 10% w/w total curcuminoids, not less than 5% punicalagins, and not less than 20% total pomegranate polyphenols. In an embodiment, a combination of the present invention comprises not less than 11.5% w/w total curcuminoids, not less than 15% punicalagins, and not less than 25% total pomegranate polyphenols. In an embodiment, a composition of the present invention comprises 20-30% total pomegranate polyphenols, 3-5% bis and dimethoxy curcumin, 12-13% curcumin, 9-30% punicalagins, 15-20% stearic and palmitic acid, 2% ascorbyl palmitate, 12-18% dextrin, 20% polysaccharides, and 7-8% phosphatidylcholine (PC). In an embodiment, a composition of the present invention is Restoridyn®, comprising 20-32% total pomegranate polyphenols, 3-5% bis and dimethoxy curcumin, 12-13% curcumin, 9-30% punicalagins, 10-16% stearic and palmitic acid, 1-2% ascorbyl palmitate, 10-16% dextrin, 15-20% polysaccharides, and 1-3% lecithin (phosphatidylcholine (PC)). In another embodiment, a composition of this invention comprises 24-30% total pomegranate polyphenols, 3-5% bis and dimethoxy curcumin, 12-13% curcumin, 9-30% punicalagins, 15-20% stearic and palmitic acid, 2% ascorbyl palmitate, 12-18% dextrin, 20% polysaccharides, and 7-8% phosphatidylcholine (PC). In another embodiment, a composition of the present invention, for instance in powdered form, comprises 13.52% curcuminoids, 1.01% ascorbyl palmitate, 2.16% phosphatidylcholine (lecithin), 16.31% dextrin, 1.15% silica, 15.85% stearic acid and palmitic acid, 15% punicalagin, 20% total pomegranate polyphenols (or total polyphenols overall), 15% polysaccharides and carbohydrates.

In an embodiment, a composition of the present invention comprises equal parts (50% w/w) of the curcumin and pomegranate extracts in Table 1, in powdered form, blended together:

TABLE 1

Composition	
Curcumin Extract	Pomegranate Extract
25-35% <i>Curcuma longa</i> extract 10-20% lecithin	100% <i>Punica granatum</i> extract of fruit Standardization: not less than 30% punicalagins and not less than 50% total polyphenols
19-35% stearic acid or salts of stearic acid 19-27% maltodextrin 1-3% ascorbyl palmitate 0.3-3% silicon dioxide Standardization: Not less than 23.00% total curcuminoids	

In an embodiment, the Curcumin Extract above is Longvida® and the Pomegranate Extract above is Pomella®. In an embodiment, the composition above has a bio-marker specification of not less than 10% total curcuminoids and not less than 10% punicalagins. Composition component lecithin may be for instance sunflower or soy lecithin. Compositions of the present invention include compositions comprising the standards described above.

In an embodiment, a composition of the present invention comprises equal parts of the curcumin and pomegranate extracts of Table 2, a solution dispersible formulation in powdered form, blended together:

TABLE 2

Composition	
Curcumin Extract	Pomegranate Extract
20-35% <i>Curcuma longa</i> extract 19-35% maltodextrin	100% <i>Punica granatum</i> extract of fruit Standardization: not less than 10% punicalagins and not less than 40% total polyphenols
1-35% stearic acid, DHA, or calcium stearate 10-20% lecithin	
1-4% ascorbyl palmitate 0.3-3% silicon dioxide Standardization: Not less than 21.00% total curcuminoids	

In an embodiment, the Curcumin Extract above is Longvida® and the Pomegranate Extract above is Pomella®. In an embodiment, the composition above has a bio-marker specification of not less than 10% total curcuminoids, not less than 3% punicalagins, and not less than 20% total polyphenols. Composition component lecithin may be for instance sunflower or soy lecithin. Compositions of the present invention include compositions comprising the standards described above.

In an embodiment, a composition of the present invention is in solid form and includes a particle size of NLT 95% through 20 mesh and NMT 45% thru 100 mesh or NLT 98% through 100 mesh.

A composition according to the present invention may be administered in a daily dose of a combination of a curcumin extract and a pomegranate extract. In an embodiment, a daily dose includes at least 50 mg of a pomegranate extract of the present invention and at least 50 mg of a curcumin extract of the present invention. In an embodiment, in a human, the daily dose includes at least 50 mg to 20 g of a curcumin extract, including for instance 80 mg, 100 mg, 200 mg, 400 mg, 500 mg, 800 mg, 1000 mg, 1500 mg, 2000 mg, and 4000 mg of curcumin extract, and any intervening

11

amounts or ranges therein, daily; and includes at least 50 mg to 5 g of a pomegranate extract, including for instance 150 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, 1000 mg, 1500 mg, 2000 mg, and 4000 mg of pomegranate extract, and any intervening amounts or ranges therein, daily.

Combinations of a pomegranate extract and a curcumin extract of the present invention may include amounts in the ratios described below. A combination and/or composition of the present invention may comprise a ratio in a range of 1:5 to 5:1 curcumin:pomegranate. For instance, this range may be directed to a ratio of 1 part curcumin to 1 part, 2 parts, 3 parts, 4 parts, or 5 parts pomegranate; 2 parts curcumin to 1 part, 2 parts, 3 parts, 4 parts, or 5 parts pomegranate; 3 parts curcumin to 1 part, 2 parts, 3 parts, 4 parts, or 5 parts pomegranate; 4 parts curcumin to 1 part, 2 parts, 3 parts, 4 parts, or 5 parts pomegranate; or 5 parts curcumin to 1 part, 2 parts, 3 parts, 4 parts, or 5 parts pomegranate. Similarly, this range may be directed to a ratio of 1, 2, 3, 4, or 5 parts curcumin to 1 part pomegranate extract; 1, 2, 3, 4, or 5 parts curcumin to 2 parts pomegranate extract; 1, 2, 3, 4, or 5 parts curcumin to 3 parts pomegranate extract; 1, 2, 3, 4, or 5 parts curcumin to 4 parts pomegranate extract; or 1, 2, 3, 4, or 5 parts curcumin to 5 parts pomegranate extract. Ratios of the present claims may include fractional parts, such as 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9; 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9; and so forth. In an embodiment, a composition of this invention is Restoridyn® (Verdure Sciences, Noblesville IN), providing equal parts (1:1 ratio of the present invention) of an optimized curcumin extract (Longvida®; Verdure Sciences, Noblesville IN) and a pomegranate extract (Pomella®; Verdure Sciences, Noblesville IN). In an embodiment, a combination of the present invention is a 2:3 blend of curcumin extract such as Longvida®:pomegranate extract such as Pomella®. In an embodiment, a combination of the present invention is a 2:3 blend of pomegranate extract such as Pomella®:curcumin extract such as Longvida®.

In an embodiment, the combination of curcumin extract and pomegranate extract of the present invention is administered orally as a prebiotic composition to improve gut health. Without being bound by theory, gut health is improved because the richness in punicalagins can stimulate the growth of colon bacteria, combined with a very low content of free ellagic acid, which may inhibit microbial growth. A composition of the present invention may be a prebiotic therefore. As mentioned above, in a pomegranate extract of the present invention, the ratio of punicalagins: free ellagic acid (w/w) is in the range of 10:1 to 35:1. For use in the present invention, such as a prebiotic, in an embodiment, the ratio of punicalagins:free ellagic acid (w/w) is about 25:1 to about 35:1.

A pomegranate extract of this invention does not include simple pomegranate juice. The commercially available best pomegranate juice contains between 2400-4000 mg/L total polyphenols (expressed as gallic acid equivalent) including punicalagins content in the range of 500-2000 mg/L. Said juice has a Brix of 16 and can be subsequently concentrated about 5 times thereby in punicalagins content, never reaching more than 10 g/L (1% w/w). Regarding the ratio of punicalagins/free ellagic acid in pomegranate juice, such did not exceed 8:1, and is further reduced due to the hydrolysis suffered by complex ellagitannins such as punicalagins, with the subsequent liberation of free ellagic acid.

In an embodiment, a composition of the present invention is a prebiotic composition, and/or a dietary supplement. Delivery systems and formulations for curcumin or other

12

substances including components of a pomegranate extract of this invention include lipid micelles, microencapsulated oils, solid lipid nanoparticles, gel, capsules, powders and other solid forms, and liquid forms.

In the present application, an “effective amount” of a composition of this invention refers to an amount of curcumin extract and pomegranate extract combined needed to reach a subject’s bloodstream and/or tissues and to improve the immune system of the subject’s body, for instance by increasing the subject’s immune response (e.g. bodily, or total body immune response, or a regionalized or localized response) or increasing the body’s ability to respond to foreign antigens or microbes and the like. In an embodiment, an effective amount of curcumin extract and pomegranate extract combined is a daily dose including at least 50 mg to 20 g of a curcumin extract such as the optimized curcumin extract Longvida®, including for instance 80 mg, 100 mg, 150 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, 1000 mg, 1500 mg, 2000 mg, and 4000 mg of curcumin extract, and any intervening amounts or ranges therein, daily; and at least 50 mg to 20 g of a pomegranate extract, including for instance 80 mg, 100 mg, 150 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, 1000 mg, 1500 mg, 2000 mg, and 4000 mg of a pomegranate extract such as Pomella®, and any intervening amounts or ranges therein, daily. In an embodiment, an effective amount of curcumin is about 100-2000 nM (0.1-2 micromolar) curcumin in blood or tissue. In an embodiment, plasma levels of curcumin are about 0.25-0.5 micromolar.

A “dietary supplement” according to the present invention refers to a composition comprising curcumin extract and pomegranate extract of the present invention which is administered as an addition to a subject’s diet, which is not a natural or conventional food, and which when administered is delivered to the bloodstream and/or bodily tissues of a subject and interacts therewith to effectively increase an immune response over a period of time. In an embodiment, a dietary supplement containing an effective amount of a composition according to the present invention is administered orally. In an embodiment, the dietary supplement is administered daily to a subject; in an embodiment, the dietary supplement is administered daily for 30 days or more, or for another period of time. A dietary supplement may be formulated into various forms, as discussed throughout this application. In an embodiment, the subject self-administers a dietary supplement of the present invention.

A composition of the present invention, including a dietary supplement of the present invention, may for instance be in the form of a sachet, tablet, capsule, powder, liquid, lozenge, chew, gummy, transdermal, injectable, etc. using standard excipients and formulation techniques in the industry. For instance, as shown in Tables 1 and 2, a composition of this invention may include lecithin, phosphatidylcholine (including lecithin as phosphatidylcholine), DHA, stearic acid/stearate, palmitic acid, dextrin, maltodextrin, ascorbyl palmitate, polysaccharides, carbohydrates, silica, and/or silicon dioxide, for instance in the ranges noted in the Tables. In an embodiment, a composition is formulated for oral administration, however, other forms of administration including injection, inhalation, and the like, may be used in the present methods.

“Administering” or “administration” of a composition of the present invention or the like refers to introducing the composition into the body of the human or other mammalian subject, so that the curcumin and pomegranate extract components are delivered to the subject’s bloodstream and/or tissues, exposing the tissues to the curcumin and pomegran-

13

ate extracts, so that the curcumin and pomegranate extracts may change the tissues from their pre-administration state as indicated throughout this application. In an embodiment, administration to a subject is oral, for instance as discussed throughout this application. Administration of a composition according to this invention may be for a period of time of 1 day, 1-7 days, 1-4 weeks, 1 month, 27-35 days, 2 months, or longer.

Supporting immune health according to the present invention, and the like, refers to helping the immune system of the subject's body maintain a healthy status. Improving immune health refers to helping the immune system of the subject's body respond to an invader in a superior manner than pre-administration, for instance by increasing the subject's immune response to a normal healthy state or to an enhanced healthy state (e.g. bodily, or total body immune response, or a regionalized or localized response) or increasing the body's ability to respond to foreign antigens or microbes and the like. Supporting and/or improving immune health may include for instance making necessary components for an immune response available or more plentiful, including but not limited to protein or RNA availability, so that an immune response may proceed for instance in optimal time in response to an invader; or otherwise may refer to preparing the subject's body for an immune challenge.

"Health" according to the present invention generally refers to systems, organs, tissues including the blood and bloodstream of the subject, and/or cells, that are functioning properly, and that are regular and intact.

An immune-related disorder according to the present invention refers to an abnormally low immune response in a subject, and an immune-related disease refers to a decrease in the body's ability to fight invaders, causing the subject to be vulnerable to invaders. In an embodiment, the immune-related disorder or disease refers to an abnormally high, or overactive, immune response in a subject; or an excessive immune response in a subject. In an embodiment, the disease or disorder treated according to the present invention is an auto-immune disease.

Treating or preventing an immune disease or disorder according to the present invention, or a symptom thereof, refers to improving the immune system of the subject's body to overcome the disease or disorder, or a symptom of the disease or disorder, for instance by increasing the subject's immune response (e.g. bodily, or total body immune response, or a regionalized or localized response) or increasing the body's ability to respond to foreign antigens or microbes and the like, in a subject having an immune-related disorder or disease (i.e. treating the disease), and/or in a subject at risk for the disease or disorder or that may develop the disease or disorder (i.e. preventing the disease). In an embodiment, a composition of the present invention may be used as an antiviral agent, immunostimulant, immunosuppressant, to treat sepsis, to treat cardiovascular diseases, and to treat respiratory diseases.

In an embodiment, reducing risk of infection according to this invention may include treating or preventing a disease cause by a virus or bacteria, for instance such as treating or preventing infection with SARS-CoV2 virus, or COVID-19.

A subject of the present invention is in an embodiment a human, but may be a mammal, including for instance a horse, cat, or dog. Individuals described in Table 3 are examples of subjects of the present invention. A healthy subject has normal bodily functions for instance falling within normal ranges of a medical blood analysis, subjectively feels in good health, and/or is not currently suffering from an infection. A sick or unwell subject has abnormal

14

bodily functions such as elevated white blood cell counts or other signs of infection or other illness for instance per a medical blood analysis, subjectively does not feel in good health, and/or currently has an infection.

The present invention may be further understood in connection with the following Examples and embodiments. The following non-limiting Examples and embodiments described throughout this application are provided to illustrate the invention.

10

Example 1

Materials & Methods

15 Experimental Design

The present study was conducted using two experiments that included a similar group of subjects (trained runners), but different sets of outcome measurements. Experiment One involved the use of Luminex bead-based methods to 20 measure changes in protein and RNA biomarkers that have been shown to be involved in the inflammatory process and muscle injury (Supplementary Table 1). The bead-based RNA biomarker panel (mRNA and lncRNA, 40 plex) was designed to complement the proteins measured (Supplementary Table 2). Experiment Two involved the use of a commercially available NanoString® array to measure and expand the set of RNA biomarkers (>500 plex) (Supplementary Table 3). Supplementation conditions (i.e. administration of the combination of curcumin extract and pomegranate extract and control) and blood sample collection time points (i.e. pre-race, 4-hour post-race, and 24-hour post-race) were identical between the two experiments.

Subjects orally self-administered a 50-50 blend of optimized curcumin (Longvida®) and pomegranate extract (Pomella®); (together, Restoridyn®; Verdure Sciences; Noblesville IN). The optimized curcumin (Longvida®) was a solid lipid curcumin particle formulation designed to improve bioavailability of at least unglucuronidated curcumin. The formulation of pomegranate extract (Pomella®) was 30 designed to provide high levels of ellagitannins, in particular punicalagins. The composition administered to the subjects comprised 20-32% total pomegranate polyphenols, 3-5% bis and dimethoxy curcumin, 12-13% curcumin, 9-30% punicalagins, 10-16% stearic and palmitic acid, 1-2% ascorbyl palmitate, 10-16% dextrin, 15-20% polysaccharides, and 1-3% lecithin (phosphatidylcholine (PC)).

During the first 26 days, subjects were supplemented daily with 1000 mg/d Restoridyn® and an additional booster dose (1000 mg/d of Restoridyn®) within one hour of completing a run longer than 6 miles (6±2 total booster doses consumed). At day 27 (3 days prior to the half-marathon race), subjects increased their daily dosage to 2000 mg/d and discontinued the use of booster doses. The subjects continued this higher dose through the 24-hour post-race blood 50 sample (day 31). The dosage was doubled on days 27-31 to manage the expected increase in muscle injury from the half-marathon race which is consistent with previous laboratory-based studies [McFarlin et al., *Reduced inflammatory and muscle damage biomarkers following oral supplementation with bioavailable curcumin. BBA Clin. 5: 72-8 (2016); Nicol et al., Curcumin supplementation likely attenuates delayed onset muscle soreness (DOMS) Eur J Appl Physiol 115(8): 1769-77(2015)*]. Venous blood samples were collected pre-race (PRE), 4-hour post-race (4 H), and 24-hour 55 post-race (24 H). These sample time points were selected to focus on the acute response to a half-marathon race [Gary et al., *Combined bead-based multiplex detection of RNA and*

protein biomarkers: Implications for understanding the time course of skeletal muscle injury and repair Methods 158: 92-96 (2019); Tanner et al., *Combining single molecule counting with bead-based multiplexing to quantify biological inflammation time course following skeletal muscle injury* Methods 158:77-80 (2019)].

Subjects

Prior to any research being conducted our study was reviewed and approved by the UNT Institutional Review Board (IRB). All study procedures were conducted in accordance with the *Declaration of Helsinki*. Subjects gave written and verbal consent to participate. Prior to enrollment, subjects were screened for contraindications to exercise and when necessary received medical clearance from a physician to participate. Subjects were stratified to one of two supplement conditions: curcumin+pomegranate (the combination of curcumin extract and pomegranate extract; Restoridyn®; N=8) or open-label control (N=10). Qualified subjects were currently training for a half-marathon race, had no significant medical history (i.e. smoking, chronic disease, etc.) and had not consumed curcumin/turmeric or pomegranate containing foods or nutritional products within the past 2-months. Body composition was measured using dual-energy x-ray absorptiometry (DEXA). Subject characteristics are reported in Table 3.

TABLE 3

Subject Characteristics		
Gender	Control Male = 5, Female = 5	Treatment Male = 5, Female = 3
Age (yr)	38.7 ± 6.0	37.8 ± 6.4
Height (cm)	176.6 ± 10.4	177.1 ± 7.1
Weight (kg)	75.6 ± 14.7	81.0 ± 14.5
Body Fat (%)	27.1 ± 10.8	26.7 ± 12.1
Body Mass Index (BMI)	24.0 ± 2.7	25.7 ± 3.3

Data reported as mean ± standard deviation. No significant difference between conditions.

Blood Collection & Isolation:

Whole blood was collected from a peripheral arm vein into Z-serum separator vacutettes (Greiner Bio-One, Kremsmünster, Austria) or PAXgene® RNA stabilizing vacutainers (PreAnalytiX, Hombrechtikon, Switzerland). According to manufacturer guidelines, PAXgene® tubes were mixed by inversion and stored at -20° C. for 24-hour, before being transferred to -80° C. for long-term storage. Individual serum aliquots were isolated by centrifugation and frozen (-80° C.) until analysis.

Experiment One: Bead-Based Analysis

Previously frozen serum samples were analyzed in duplicate for protein concentration using commercially available bead-based kits (Supplementary Table 1): high sensitivity cytokines (Milliplex®; Millipore-Sigma; St. Louis, MO; 21-cytokines), soluble cytokine receptors (Milliplex®; Millipore-Sigma; 14-soluble receptors), and myokines (Milliplex®; Millipore-Sigma; 15-myokines). All analysis was conducted according to manufacture guidelines, raw data was collected using a bead-based multiplex analyzer (FlexMAP 3D™). PAXgene® blood was processed and analyzed for RNA expression in duplicate using custom extraction and bead-based gene expression kits (QuantiGene; ThermoFisher Scientific; Santa Clara, CA; 40-RNA) (Supplementary Table 2). Sample processing and analysis was completed according to the manufacture guidelines. After the assay was complete, raw data was collected using a bead-based multiplex analyzer (FlexMAP 3D™; Luminex Corp; Austin, TX).

Experiment One: Statistical Analysis

Protein biomarker concentrations were calculated using commercially available software (Milliplex® Analyst v5; MilliporeSigma) that automatically calculated unknown values compared to a standard curve. R2 for all standard curves were >0.98. RNA data was normalized by dividing the median fluorescent intensity for a given RNA target by the geometric mean of the control RNA median fluorescent intensity. Data were cleaned and analyzed using R (version 3.6.0). The statistical analysis of the pairwise comparisons ("Curcumin+Pomegranate" versus "Control") was done with the ggpubr package (version 0.2) and a Welch t-test. The data was visualized using the ggplot2 package (version 3.1.0). To visualize significantly regulated proteins/RNAs volcano plots were used with a fold-change cutoff of 1.2 and a p-value cutoff of 0.05 displayed as dashed lines. Analyte label saturation indicates test-power where full saturation indicates >0.8 test-power.

Experiment Two: Nanostring Analysis

Total RNA was extracted from frozen PAXgene® blood using a commercial isolation kit (PAXgene® Blood miRNA kit; PreAnalytiX, Hombrechtikon, Switzerland) using an automated system (QIAcube; Qiagen, Hilden, Germany). Isolated total RNA was analyzed using a Human Immunology Panel (nCounter; Nanostring, Seattle, WA, 594-RNA) (Supplementary Table 3), raw data was acquired using a multiplex imaging system (Sprint Profiler; NanoString®, Seattle, WA). Samples were processed according to the manufacture guidelines. The raw data included total counts of each target mRNA present in each sample.

Experiment Two: Statistical Analysis

Quality control and assay performance analyses were conducted on all raw mRNA data using nSolver software (NanoString®) with the nCounter Advanced analysis module (v.2.0.115). Target mRNA data was normalized to internal control/housekeeping mRNA (TUBB, GUSB, TBP, PPIA, SDHA, POLR1B, ALAS1, HPRT1, EEF1G, RPL19, ABCF1, G6PD, POLR2A, and GAPDH). Normalized data were cleaned and analyzed using R (version 3.6.0). The statistical analysis of the pairwise comparisons ("Curcumin+Pomegranate" versus "Control") was done with the ggpubr package (version 0.2) and a Welch t-test. The data was visualized using the ggplot2 package (version 3.1.0). To visualize significantly regulated mRNA, we used volcano plots with a fold-change cutoff of 1.2 and a p-value cutoff of 0.05 displayed via dashed lines. Analyte label saturation indicates test-power where full saturation indicates >0.8 testpower.

Results

Experiment One: Protein Analysis

Volcano plots were generated based on log 2 median ratios and negative decadic logarithm of the p-value to identify target protein abundances that were either increased, decreased, or not altered when comparing the supplement to the control (FIG. 1). Additional box and whisker plots of the absolute concentration of the proteins in the blood were generated to confirm proteins that significantly changed with supplement relative to control (FIG. 2; from top, row 1: BDNF, IL-10, IL-13, IL-4, IL-8; row 2: ITAC, MIP-1alpha, MIP-3alpha, sgp130, sIL-2Ralpha; row 3: TNF-alpha). At PRE, prior to the race, IL-10, TNF-alpha, IL-8, ITAC, IL-13, MIP-1alpha, and MIP-3alpha abundance were found significantly increased in the supplement group when compared to the control group, while BDNF and sgp130 were found in significantly lower levels. At 4 H, 4

hours post-race, IL-10 was found in higher levels and BDNF was found in lower levels and at 24 H, 24 hours post-race, IL-4, sIL-2Ralpha, and IL-8 abundance were increased when supplement was compared to the control group. There were no proteins found in lower levels at 24 H.

Experiment One: Bead-Based RNA Analysis

Volcano plots were generated based on log 2 median ratios and negative decadic logarithm of the p-value to identify bead-based RNA that were either up-regulated, down-regulated, or not changed with supplement compared to control (FIG. 3). Additional box and whisker plots were generated to confirm RNA that significantly changed with supplement (FIG. 4; from top, row 1: CCL22, CX3CL1, GUSB, IL10, IL6; row 2: IL6R, IL7R, IL8, LINC00305, MYD88; row 3: NKILA, PTGES, PTGS2, THRIL, TLR2; row 4: TNFRSF1A, TNFRSF1B, TNFSF14, TRAF6). At PRE, no RNA was significantly up-regulated but IL-6, IL-10, PTGES, THRIL, LINC00305, TNFSF14, TRAF6, and NKILA were significantly down-regulated with supplement compared to control. At 4 H, the RNA that were significantly up-regulated were MYD88, TNFRSF1B, TNFRSF1A, TLR2, IL-6R, and PTGS2; the down-regulated RNAs were IL-6, IL-10, PTGES, THRIL, LINC00305, CCL22, IL-7R, and CX3CL1 with supplement compared to control. At 24 H, the RNA that was significantly up-regulated was GUSB while IL-6, IL-10, PTGES, TRAF6, LINC00305, IL-8, and TLR2 were down-regulated with supplement compared to control.

Experiment Two: Nanostring mRNA Analysis

Volcano plots were generated based on log fold change to identify NanoString® mRNA that were either up-regulated, down-regulated, or not changed with supplement compared to control (FIG. 5). At PRE, the mRNA that were significantly upregulated were ARG2, EDNRB, LILRB5, C4A/B, CSF2, RAG1, THY1, CD55, IL17A, and CXCL13 with supplement compared to control. Significantly, curcumin and pomegranate for endurance running down-regulated mRNA at PRE with supplement were CX3CR1, IKZF1, IL2RG, PECAM1, and CD81. At 4 H, the mRNA that were significantly up-regulated were HAMP, MBL2, CASP3, B2M, KLRF2, PDCD1LG2, GPR183, MRC1, and CD3D. There was no significantly down-regulated mRNA at 4 H with supplement compared to control. At 24 H, GATA3 mRNA was significantly upregulated and MASP1 was down-regulated with supplement compared to control.

DISCUSSION

The purpose of this study was to determine which systemic inflammatory proteins and RNA were altered when subjects were administered curcumin extract combined with pomegranate extract and completed a half-marathon.

Surprisingly and unexpectedly, administration of the composition containing the combined curcumin extract and pomegranate extract showed the composition supported immune function, preparing the subject's body for an immune challenge. An increase in expression of the host-pathogen interaction RNA marker ARG2 was identified, as shown in FIGS. 5 and 6. See for instance FIG. 5 ("PRE"), showing the increased fold-change in ARG2, and FIG. 6, showing significantly increased ARG2 RNA expression with the combination of curcumin extract and pomegranate extract as compared with control before the half-marathon began (PRE; p≤0.001). The ARG2 gene encodes for the protein arginase, type II, a regulator of innate and adaptive immune responses. (From top, FIG. 6 entries are, row 1:ARG2, B2M, C2, C4A/B, C5; row 2: CASP3, CD1A,

CD3D, CD55, CD81; row 3: CFI, C8F2, CX3CL1, CX3CR1, CXCL13; row 4: EDNRB, EGR2, GATA3, GPR183, HAMP; row 5: IFNA1/13, IKZF1, IL17A, IL2RG, KLRF2; row 6: LILRB5, MASP1, MBL2, MRC1, PDCD1LG2; row 7: PECAM1, RAG1, THY1, TIRAP, TNFSF18).

Also, increases in EDNRB and HAMP RNA, markers for hemostasis, may be seen in FIGS. 5 and 6 (FIG. 6 middle row, left and right plots, respectively). EDNRB RNA increased significantly for curcumin+pomegranate (the combination of curcumin extract and pomegranate extract) over control before the half-marathon began (PRE; p≤0.01), similar to ARG2, whereas HAMP RNA increased significantly for curcumin+pomegranate (the combination of curcumin extract and pomegranate extract) over control 4 hours after the subject finished the half-marathon (4 H; p≤0.05). The EDNRB gene encodes for endothelin receptor type B, and the HAMP gene for hepcidin antimicrobial peptide, both of which are markers for hemostasis, which is linked to immune function and in particular adaptive immunity.

While these changes are not associated with muscle injury, they support our claim that the combination of curcumin extract and pomegranate extract of this invention support and improve immune function, before strenuous exercise as well as the post-exercise immune system. Also, the findings support a reduced incidence of opportunistic infection that is commonly reported following strenuous endurance exercise. The changes in RNA expression following administration of the combined curcumin and pomegranate extracts of the present invention mirror changes observed with protein biomarkers.

Further investigation shows immune system changes and support for the Adaptive Immune System and the Innate Immune System, for instance as seen by changes from curcumin+pomegranate (the combination of curcumin extract and pomegranate extract) administration in RNA expression relating to the Adaptive Immune System, Apoptosis, Autophagy, B Cell Receptor Signaling, Cell Adhesion, Chemokine Signaling, Complement System, Cytokine Signaling, Hemostasis (EDNRB and HAMP), Host-Pathogen Interaction (ARG2), Immunometabolism, Inflammasomes, Innate Immune System, Lymphocyte Activation, Lymphocyte Trafficking, MHC Class I Antigen Presentation, MHC Class II Antigen Presentation, NF-κB Signaling, NLR Signaling, Oxidative Stress, Phagocytosis and Degradation, T Cell Receptor Signaling, TGF-β Signaling, Th1 Differentiation, Th17 Differentiation, Th2 Differentiation, TLR Signaling, TNF Family Signaling, Transcriptional Regulation, Treg Differentiation, Type I Interferon Signaling, Type II Interferon Signaling, all as shown in FIG. 7.

With regard to the original goal of this study, our laboratory and others have demonstrated that supplementation with optimized curcumin alone has the potential to reduce protein inflammatory cytokines and muscle soreness following a variety of laboratory-based muscle damage tests [McFarlin et al., "Does Acute Improvement in Muscle Recovery with Curcumin Supplementation Translate to Long-term Training?" *J. Sci. Sport Exerc.* pp. 1-5 (2019)].

We observed a group of cytokines whose pre-exercise values were greater in supplement than control; however, this difference disappeared by 4-hour post-race due to an increase in the control and no change in the supplement group (IL-10, IL-13, IL-4, ITAC, MIP-1alpha, MIP-3alpha, and TNF-alpha). Further, we found no group differences in a variety of muscle damage biomarkers prior to exercise (muscle damage myokines, CK, etc.; data not shown), hence the difference between groups is likely due to individual

variability and not a supplement effect. It is notable that the control group experienced an increase in these markers (IL-10, IL-13, 11-4, ITAC, MIP-1alpha, MIP-3alpha, and TNF-alpha) at 4-hour post-race, while the supplement had no change. This later finding supports a potential effect of a blunted post-race inflammatory response with supplement. Some of the proteins had a similar exercise-induced increase at 4-hour post-race in both groups, with the only significant difference being at PRE (IL-8 and sgp130). Specific proteins that changed with supplement were associated with chemotactic signaling (ITAC, IL-8, MIP-3alpha, and MIP-1alpha), anti-inflammatory (IL-10 and IL-13), muscle recovery (BDNF), and B cell activation (sIL-2Ralpha, IL-8, and IL-4). All of these proteins have been previously reported to play a role in muscle recovery from exercise and/or injury [Gary (2019); Nicol (2015); Sciberras, J. N., et al., "The effect of turmeric (Curcumin) supplementation on cytokine and inflammatory marker responses following 2 hours of endurance cycling" *J. Int. Soc. Sports Nutr.* 12(1):5 (2015); Davis et al., "Curcumin effects on inflammation and performance recovery following eccentric exercise-induced muscle damage" *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 292(6):R2168-73 (2007); Drobnić et al., "Reduction of delayed onset muscle soreness by a novel curcumin delivery system (Meriva®): a randomised, placebo-controlled trial" *J. Int. Soc. Sports Nutr.* 11:31 (2014); McFarlin (2016); Bernecker et al., "Evidence for an exercise induced increase of TNF-alpha and IL-6 in marathon runners" *Scand. J. Med. Sci Sports* 23(2):207-14 (2013); Suzuki et al., "Changes in markers of muscle damage, inflammation and HSP70 after an Ironman Triathlon race" *Eur. J. Appl. Physiol.* 98(6):525-34 (2006)].

Explaining the protein response with supplement may partially be difficult because all the subjects were considered healthy and most commercial protein assays are optimized to measure disease associated changes (which we did not observe in the present study). Supplement was associated with no increase in proteins at 4-hour compared to control, which may be consistent with an improved response. The control response for all proteins was consistent with what our lab and others have reported following distance running. Similar to the protein cytokine response, we found a group of RNA with greater levels prior to the race with supplement compared to control, but this difference was not present at 4-hour post-race due to an increase in the control group response and no change with supplement (CCL22, GUSB, IL-6, LINC00305, NKILA, PTGES, THRIL, TRAF6, ARG2, CD1A, CD55, CFI, CSF2, CX3CL1, CX3CR1, EDNRB, GATA3, LILRB5, THY1, and TIRAP). The pre-exercise difference may or may not be due to individual variability rather than a supplement effect due to no differences in muscle injury markers measured (muscle damage myokines, CK, etc.; data not shown). Some RNA were increased at 4-hour post-race regardless of condition (IL-10, IL-6R, MYD88, PTGS2, TLR2, TNFRSF1A, TNFRSF1B, TNFSF14, B2M, C2, C4A/B, CASP3, EGR2, HAMP, IFNA1/B, IKZF1, IL-17A, IL2RG, KLRF2, MASP1, MBL2, MRC1, PDCD1LG2, PECAM1, RAG1, TNFSF15). The RNA that changed with supplement were associated with TNF α (TNFSF14, TRAF6, and THRIL), nuclear factor kappa beta (NF- κ B) signaling pathway (NKILA and LINC00305), inflammation-associated RNA (IL-10, IL-6, PTGES, TLR2, IL7R, CX3CL1, CCL22, IL-8, CSF2, RAG1, IL-17A, IL2RG, CX3CR1, CASP3, B2M, GATA3, LILRB5, C4A/B, PECAM1, MASP1, MBL2, CD55, THY1, IKZF1, PDCD1LG2, and KLRF2), and anti-inflammatory RNA (TNFRSF1A, TNFRSF1B, and IL-6R).

Similar to the protein response, supplementation resulted in no change in certain RNA at 4-hour, compared to an increased response with control, which may be consistent with an improved response. Interestingly, as discussed above, we also detected changes in host-pathogen interaction (ARG2) and hemostasis (EDNRB and HAMP). While these responses are not associated with muscle injury their change support an improved post-exercise immune system and reduced incidence of opportunistic infection that is commonly reported following strenuous endurance exercise [McFarlin et al., "Baker's yeast beta glucan supplementation increases salivary IgA and decreases cold/flu symptomatic days after intense exercise" *J. Diet. Suppl.* 10(3):171-183 (2013); Bergendiova et al., "Pleuran (beta-glucan from *Pleurotus ostreatus*) supplementation, cellular immune response and respiratory tract infections in athletes" *Eur. J. Appl. Physiol.* 111(9):2033-2040 (2011); Gleeson et al., "Respiratory infection risk in athletes: association with antigen-stimulated IL-10 production and salivary IgA secretion" *Scand. J. Med. Sci. Sports* 22(3):410-417 (2012); Gleeson et al., "Influence of training load on upper respiratory tract infection incidence and antigen-stimulated cytokine production" *Scand. J. Med. Sci. Sports* 23(4):451-457 (2013)]. In summary, the observed supplement-associated changes in RNA mirror the changes observed with protein biomarkers, and show that the present compositions support immune health.

It is well documented that reduced post-exercise inflammation is associated with a faster return to normal function in activities of daily living or training [Bell et al., "Recovery facilitation with Montmorency cherries following high-intensity, metabolically challenging exercise" *Appl. Physiol. Nutr. Metab.* 40(4):414-23 (2015); McLeay et al., "Effect of New Zealand blueberry consumption on recovery from eccentric exercise-induced muscle damage" *J. Int. Soc. Sports Nutr.* 9(1):19 (2012); Michailidis et al., "Thiol-based antioxidant supplementation alters human skeletal muscle signaling and attenuates its inflammatory response and recovery after intense eccentric exercise" *Am. J. Clin. Nutr.* 98(1): 233-45 (2013)].

The findings of the present study are consistent with previously reported reductions in post-exercise inflammation. When combining all the biomarker responses, a similar pattern was observed where supplement was associated with no change at 4-hour, which is consistent with a blunted post-exercise response compared to control. By extension it is reasonable to speculate that combined supplementation with optimized curcumin and a pomegranate extract may be useful as part of a comprehensive plan designed to mitigate post-exercise inflammation/injury and improve subsequent recovery between sessions.

In FIG. 1, the volcano plots display the group comparison log 2 median ratios (Curcumin+Pomegranate/Control) of protein biomarker data and the log 10-p-value of the Welch t-test (horizontal dashed line: p-value=0.05; vertical dashed lines: fold-change=1.2) at prerace (PRE), 4-hour post-race (4 H), and 24-hour post-race (24 H). Significantly up-regulated protein biomarkers with supplement compared to control are discussed in the Results section above, as are significantly down-regulated protein biomarkers with supplement compared to control. Biomarker label color saturation indicates test-power (saturated=test-power >0.8). Boxes (shown with dotted lines) indicating test-power ≤ 0.8 (top to bottom, PRE: IL-13, MIP-1alpha, BDNF, MIP-3alpha, sgp130; 4 H: IL-10, BDNF; 24 H:sIL-2Ralpha, IL-8, IL-4). Multiplex protein assays were conducted using com-

mercially available bead-based kits (Milliplex®; MilliporeSigma) and multiplex analyzer (FlexMAP 3D™; Luminex Corp.).

FIG. 2 demonstrates the concentration of significantly changed protein biomarkers for supplement (black) and control (light grey) across all time points (PRE, 4 H, and 24 H). All protein concentrations are expressed as pg/mL. Observed supplement group responses were either flat (i.e. no response to exercise) or increased to a similar degree as the control group. Multiplex protein assays were conducted using commercially available bead-based kits (Milliplex®; MilliporeSigma) and multiplex analyzer (FlexMAP 3D™; Luminex Corp.). Note: Welch t-test p-value significance *($p\leq 0.05$); **($p\leq 0.01$); ***($p\leq 0.001$); ****($p\leq 0.0001$).

The volcano plots of FIG. 3 display the group comparison log 2 median ratios (Curcumin+Pomegranate/Control) of RNA data and the log 10-p-value of the Welch t-test (horizontal dashed line: p-value=0.05; vertical dashed lines: fold-change=1.2) at pre-race (PRE), 4-h post-race (4 H), and 24-hour post-race (24 H). Significantly up-regulated RNA with supplement compared to control are discussed in the Results section above, as are significantly down-regulated RNA with supplement compared to control. Biomarker label color saturation indicates test-power (saturated=test-power >0.8). Boxes (shown with dotted lines) indicating test-power ≤0.8 (top to bottom, PRE: TNFSF14, IL6, TRAF6, NKILA; 4 H: MYD88, THRIL, TNFRSF1B, IL7R, TLR2, IL6R, CX3CL1, PTGS2; 24 H: TRAF6, LINC00305, IL6, TLR2, IL8). Multiplex RNA assays were conducted using commercially available bead-based kits (Quantigene®; ThermoFisher Scientific) and multiplex analyzer (FlexMAP 3D™; Luminex Corp.).

FIG. 4 shows the normalized gMFI (geometric mean of median fluorescent intensity) of significantly changed RNA for supplement (black) and control (light grey) across all time points (PRE, 4 H, and 24 H). Observed supplement group responses were either flat (i.e. no response to exercise) or increased to a similar degree as the control group. Multiplex RNA assays were conducted using commercially available bead-based kits (Quantigene®; ThermoFisher Scientific) and multiplex analyzer (FlexMAP 3D™; Luminex Corp.). Note: Welch t-test p-value significance *($p\leq 0.05$); **($p\leq 0.01$); ***($p\leq 0.001$); ****($p\leq 0.0001$).

In FIG. 5, volcano plots display the group comparison log 2 median ratios (Curcumin+Pomegranate/Control) of mRNA data and the log 10-p-value of the Welch t-test (horizontal dashed line: p-value=0.05; vertical dashed lines: fold-change=1.2) at pre-race (PRE), 4-hour post-race (4 H), and 24-hour post-race (24 H). Significantly up-regulated RNA with supplement compared to control are discussed in the Results section above, as are significantly down-regulated RNA with supplement compared to control. Biomarker label color saturation indicates test-power (saturated=test-power >0.8). Boxes (shown with dotted lines) indicating test-power ≤0.8 (top to bottom, PRE: IKZF1, IL2RG, PECAM1, CD81, CXCL13, THY1, RAG1, IL17A; 4 H: MRC1, CASP3, MBL2, GPR183, KLRF2, B@M, CD3D; 24 H: GATA3, MASP1). Multiplex RNA assays were conducted using commercially available Human Immunology Panel (nCounter®; NanoString®) and imaging platform (Sprint Profiler; NanoString®).

FIG. 6 demonstrates the mRNA count for each significantly changed mRNA for supplement (black) and control (light grey) across all time points (PRE, 4 H, and 24 H). Observed supplement group responses were either flat (i.e. no response to exercise) or increased to a similar degree as the control group. Multiplex RNA assays were conducted

using commercially available Human Immunology Panel (nCounter®; NanoString®) and imaging platform (Sprint Profiler; NanoString®). Note: Welch t-test p-value significance *($p\leq 0.05$); **($p\leq 0.01$); ***($p\leq 0.001$); ****($p\leq 0.0001$).

Example 2

Endurance-trained men and women (26-45 years old) currently training for a half-marathon race gave Institutional Review Board (IRB) consent. Participants were assigned to Control (N=6) or Supplement (N=6). Combined curcumin and natural proprietary pomegranate extract (Restoridyn®) dietary supplements were taken in an amount of 500 mg Restoridyn® per day for 26 days. Booster doses of 1000 mg Restoridyn® per day were taken following training runs greater than 6 miles in length and 3 days prior to the half-marathon race (days 27, 28, 29). On day 29, subjects ran the half-marathon. On day 30, a booster dose was taken. Control was taken for 30 days. Restoridyn® provided to subjects was as described in Example 1.

Venous blood samples taken pre-race, 4-hours after the race, and 24-hours after the race were collected in PAXgene Blood RNA tubes (PreAnalytiX). Samples were incubated at room temperature then frozen until total RNA isolation and analysis was performed. Total RNA was isolated using an automated system (QIAcube) and RNA quantity and Quality was assessed with a fluorescent RNA assay and fluorometer (Qubit).

To measure RNA, a 594-plex Human Immunology Panel was analyzed on a NanoString nCounter Platform. Results were normalized to housekeeper genes. Differential expression analysis was conducted using Nanostring nSolver software. Significance was set at $p<0.05$.

See Supplementary Table 3 for further information on targets of Tables 4-7 to immune response and other embodiments of this application. Inflammation-associated mRNA expression was reduced with daily Restoridyn® administration prior to and after a half-marathon race. mRNA changes with Restoridyn® supplementation may positively affect recovery after endurance exercise and the ability to return to training more quickly.

TABLE 4

PRE-Half-Marathon		
TABLE - PRE Significant mRNA targets ($p < 0.05$)	Official Name	Upregulated/ Downregulated
CD3EAP	CD3e molecule, epsilon associated protein	Down
C4A/B	complement component 4A/complement component 4B	Up
CX3CR1	chemokine (C-X3-C motif) receptor 1	Down
TIRAP	toll-interleukin 1 receptor, domain containing adaptor protein	Up
TNFSF4	tumor necrosis factor (ligand) superfamily, member 4	Up
IRAK3	interleukin-1 receptor-associated kinase 3	Up
RAG1	recombination activating gene 1	Up

TABLE 4-continued

PRE-Half-Marathon		
Significant mRNA targets (p < 0.05)	Official Name	Upregulated/Downregulated
IL2RG	interleukin 2 receptor, gamma	Down
TNFSF15	tumor necrosis factor (ligand) superfamily, member 15	Up
CD55	CD55 molecule, decay accelerating factor for complement	Up
ARG2	arginase, type II	Up
C5	complement component 5	Up
TNFSF8	tumor necrosis factor (ligand) superfamily, member 8	Up
PTK2	PTK2 protein tyrosine Kinase 2	Up
FKBP5	FK506 binding protein 5	Up
C6	compliment component 6	Up
TNFRSF17	tumor necrosis factor receptor superfamily, member 17	Up
ITGAE	integrin, alpha E	Up
ARG1	arginase, liver	Up
C1S	complement component 1, s subcomponent	Up
GP1BB	glycoprotein 1b (platelet), beta polypeptide	Up
GATA3	GATA binding protein 3	Up
CD24	CD24 molecule	Up
FOXP3	forkhead box P3	Up

TABLE 5

4 Hours after Half-Marathon		
Significant mRNA targets (p < 0.05)	Official Name	Upregulated/Downregulated
IL28A	interleukin 28A (interferon, lambda 2)	Down
CSF1	colony stimulating factor 1 (macrophage)	Down
BAX	BCL2-associated X protein	Down
IFITM1	interferon induced transmembrane protein 1	Up
GPR183	G protein-coupled receptor 183	Up
CXCL12	chemokine (C-X-C motif) ligand 12	Up
CASP3	caspase 3, apoptosis-related cysteine peptidase	Up
CASP2	caspase 2, apoptosis-related cysteine peptidase	Down
PDCD1	programmed cell death 1	Down
LY96	lymphocyte antigen 96	Up
CD3D	CD3d molecule, delta (CD3-TCR complex)	Up
B2M	Beta-2-microglobulin	Up
C9	complement component 9	Down
XCR1	chemokine (C motif) receptor 1	Down

TABLE 5-continued

4 Hours after Half-Marathon		
Significant mRNA targets (p < 0.05)	Official Name	Upregulated/Downregulated
IL1RL1	interleukin 1 receptor-like 1	Down
PIGR	polymeric immunoglobulin receptor	Down
HFE	hemochromatosis	Down
ZAP70	zeta-chain (TCR) associated protein kinase 70 kDa	Down
BTLA	B and T lymphocyte associated	Down
CD96	CD96 molecule	Down
TLR5	Toll-like receptor 5	Up
SELL	Selectin L	Up
CEACAM1	Carcinoembryonic antigen-related cell adhesion molecule	Up
ENTPD1	Ectonucleoside triphosphate diphosphohydrolase 1	Up
GNLY	Granulysin	Down
TLR4	Toll-like receptor 4	Up
STAT3	Signal transducer and activator of transcription 3 (acute phase response factor)	Up
KLRC4	Killer cell lectin-like receptor subfamily C, member 4	Down
CD247	CD247 molecule	Down
CR1	Complement component (3b/4b)	Up
STAT5A	receptor 1 Knops blood group	
BST1	Signal transducer and activator of transcription 5A	Up
CLEC5A	Bone marrow stromal cell antigen 1	Up
IFI16	C-type lectin domain family 5, member A	Up
FCGR3A/B	Interferon, gamma-inducible protein 16	Up
Fo fragment of IgG, low affinity IIIa, receptor (CD16a)/Fc fragment of IgG, low affinity IIIb, receptor (CD16a)		
LILRA3	Leukocyte immunoglobulin-like receptor, subfamily A, member 3	Up
LILRA2	Leukocyte immunoglobulin-like receptor, subfamily A, member 2	Up
CFP	Complement factor properdin	Up
SLAMF7	SLAM family member 7	Down
MYD88	Myeloid differentiation primary response gene (88)	Up

TABLE 6

Restoridyn ® (24 H after half-marathon)		
Significant mRNA targets* (p < 0.01)	Official Name	Upregulated/Downregulated
ZAP70	zeta-chain (TCR) associated protein kinase 70 kDa	Down
CD96	CD96 molecule	Down
TLR5	Toll-like receptor 5	Up
SELL	Selectin L	Up
CEACAM1	Carcinoembryonic antigen-related cell adhesion molecule	Up
ENTPD1	Ectonucleoside triphosphate diphosphohydrolase 1	Up
GNLY	Granulysin	Down
TLR4	Toll-like receptor 4	Up
STAT3	Signal transducer and activator of transcription 3 (acute phase response factor)	Up
KLRC4	Killer cell lectin-like receptor subfamily C, member 4	Down
CD247	CD247 molecule	Down
CR1	Complement component (3b/4b)	Up
STAT5A	receptor 1 Knops blood group	
BST1	Signal transducer and activator of transcription 5A	Up
CLEC5A	Bone marrow stromal cell antigen 1	Up
IFI16	C-type lectin domain family 5, member A	Up
FCGR3A/B	Interferon, gamma-inducible protein 16	Up
Fo fragment of IgG, low affinity IIIa, receptor (CD16a)/Fc fragment of IgG, low affinity IIIb, receptor (CD16a)		
LILRA3	Leukocyte immunoglobulin-like receptor, subfamily A, member 3	Up
LILRA2	Leukocyte immunoglobulin-like receptor, subfamily A, member 2	Up
CFP	Complement factor properdin	Up
SLAMF7	SLAM family member 7	Down
MYD88	Myeloid differentiation primary response gene (88)	Up

TABLE 6-continued

Restoridyn® (24 H after half-marathon)		
Significant mRNA targets* (p < 0.01)	Official Name	Upregulated/ Downregulated
TNFSF10	Tumor necrosis factor (ligand) superfamily, member 10	Up
CD58	CD58 molecule	Up

*Top 25 targets listed

TABLE 7

CONTROL (24 H after half-marathon)		
Significant mRNA targets* (p < 0.01)	Official Name	Upregulated/ Downregulated
PLAUR	Plasminogen activator, urokinase receptor	Up
FCGR3A/B	Fc fragment of IgG, low affinity IIIa, receptor (CD16a)/Fc fragment of IgG, low affinity IIIb, receptor (CD16a)	Up
IGF2R	Insulin-like growth factor 2 receptor	Up
LILRA3	Leukocyte immunoglobulin-like receptor, subfamily A, member 3	Up
ZAP70	Zeta-chain (TCR) associated protein kinase 70 kDa	Down
TRAF3	TNF receptor-associated factor 3	Down
BCL6	B-cell CLL/lymphoma 6	Up
FCGR2A/C	Fc fragment of IgG, low affinity IIa, receptor (CD32)/Fc fragment of IgG, low affinity IIc, receptor for (CD32)	Up
ICAM3	Intercellular adhesion molecule 3	Up
IL1RN	Interleukin 1 receptor antagonist	Up
CSF3R	Colony stimulating factor 3 receptor (granulocyte)	Up
IL6R	Interleukin 6 receptor	Up
HLA-B	Major histocompatibility complex, class I, B	Up
LILRA2	Leukocyte immunoglobulin-like receptor, subfamily A, member 2	Up
ENTPD1	Ectonucleoside triphosphate diphosphohydrolase 1	Up
MME	Membrane metallo-endopeptidase	Up
TNFRSF9	Tumor necrosis factor receptor superfamily, member 9	Up
STAT4	Signal transducer and activator of transcription 4	Down
TLR5	Toll-like receptor 5	Up
TLR2	Toll-like receptor 2	Up

*Top 20 targets listed

Example 3

Combination Dietary Polyphenol and Methylsulfonylmethane Supplementation Alters Systemic Inflammation Time

5 Course Response after Running a Half Marathon Race

1 Material and Methods

1.1 Participants

10 This study was approved by the University of North Texas Institutional Review Board and was executed in accordance with the Declaration of Helsinki. Fifteen subjects gave written and oral informed consent and met inclusion criteria prior to participating the study. Inclusion criteria included: (1) male or female between the ages of 20-60 years old, (2) non-smoker, (3) healthy, with no known disease as determined by medical history questionnaire (4) physically active 6-months prior to the start of the study, and (5) currently training for a half marathon race. Participants were excluded if they consumed curcumin/turmeric, pomegranate extract, and/or methylsulfonylmethane (MSM) for three or more days per week for two months prior to the start of the study. Subject characteristics can be found in Table 8.

TABLE 8

Subject characteristics			
	Control Male = 5; Female = 5	Treatment Male = 3; Female = 2	
Gender			
Age (yr)	38.7 ± 6.0	40.0 ± 2.5	
Height (cm)	179.1 ± 12.3	178.1 ± 8.3	
Weight (kg)	80.7 ± 15.2	82.8 ± 16.3	
Body Fat (%)	27.1 ± 10.8	26.1 ± 9.5	

35 Data reported as mean ± standard deviation. No significant difference between conditions.

1.2 Experimental Design

Qualifying subjects returned to the laboratory to assess body composition using dual-energy x-ray absorptiometry (DEXA) and to receive supplementation and training log instructions. Subjects were randomized to either control (n=10) or treatment (n=5) using an open label design. Subject characteristics are presented in Table 8. The treatment group consumed a combination of Restoridyn® (1000 mg/d; 50-50 mix of optimized curcumin and pomegranate extract; Verdure Sciences; Noblesville IN) and MSM (500 mg/d; Bergstrom Nutrition; Vancouver, WA) for 26 days. During this period, subjects were instructed to consume a booster dose (additional 500 mg) in addition to the daily dose when training sessions were greater than six miles. Three days prior to and one day after the half marathon race the treatment group doubled their daily dosage (i.e. 500 mg/d to 1000 mg/d). Supplement safety was assessed by measuring serum alkaline phosphatase (liver function bio-marker) was measured using an enzymatic assay (Pointe Scientific; Canton, MI) on an automated chemistry analyzer (Awareness Tech; Palm City, FL). There were no differences between conditions and values were within normal range (control: 33.1±11.9; treatment: 51.2±21.1). Venous blood samples were collected from an antecubital vein prior to (PRE), 4 hours (4 h), and 24 hours (24 h) after running a half marathon race (13.1 miles; 21.1 km).

1.3 Monitoring Exercise Training

Subjects were given access to MapMyRun (Under Armour; Baltimore, MD) to record their training sessions. Heart rate was measured using wrist-based heart rate devices (Garmin or Apple Watch) and caloric expenditure for the

training sessions was estimated by the MapMyRun app. By using this approach, we were able to monitor subject training in real-time and intervene when necessary.

1.4 Biomarker Measurement

Whole blood at PRE, 4 h, and 24 h was collected into serum separator vacuettes (Griener; Kremsmünster, Austria) and PAXgene® RNA stabilizing vacutainers (PreAnalytiX, Hombrechtikon, Switzerland). The serum samples were allowed to clot at room temperature for 20-min followed by centrifugation (20-min at 400×g). The resulting serum was stored at -80° C. until analysis. PAXgene blood was frozen at -20° C. for 24-hr then transferred to long term storage at -80° C. until RNA analysis. Prior to RNA analysis, PAX-gene blood was thawed and incubated at room temperature for 24-hours. RNA was analyzed using custom bead-based RNA kits (QuantiGene®; ThermoFisher Scientific; Santa Clara, CA). The RNA targets (41 mRNA, 6 lncRNA, and 3 controls) were chosen to complement the measured protein markers to assess skeletal muscle injury and oxidative stress. Protein markers were measured using a combination of commercially-available multiplex kits for high-sensitivity cytokines (Milliplex; Millipore-Sigma; St. Louis, MO; 21-cytokines), soluble cytokine receptors (Milliplex; Millipore-Sigma; 14-soluble receptors), and myokines (Milliplex; Millipore-Sigma; 15-myokines). Samples were processed according to manufacturer specifications and raw data files were acquired using a bead-based multiplex analyzer (FlexMap3D; Luminex Corp; Austin, TX). Prior to analysis, instrument calibration and verification were conducted according to manufacturer specifications.

1.5 Statistical Analysis

RNA data was normalized by dividing the median fluorescent intensity for a given RNA target by the geometric mean of the 3 control RNA median fluorescent intensity. Protein biomarker concentrations were calculated using commercially available software (Milliplex Analyst v5; MilliporeSigma) that automatically calculated unknown values compared to a standard curve. R² for all standard curves were >0.98. Data were cleaned and analyzed using R-studio to create volcano plots based on log change of treatment normalized to control. A two-sample Wilcoxon Test was used to analyze for significance based on a standardized fold change (1.2; P<0.05). Data were standardized into 6 volcano plots to identify biomarkers that were significantly up or down-regulated relative to control.

2 Results

2.1 Exercise Training

The goal of the present study was to identify a treatment response profile by combining the various outcome measures into a single response type. Based on the training data present above (section 2.3), the treatment response profile observed in the present study allowed for treatment subjects to train at a higher mileage and exertion level compared to controls. Specifically, as a whole the treatment group was able to complete a total of 11% more mileage (341.2±3.5 vs. 307.5±3.8 miles) and expend 20% more calories (51, 802±546 vs. 43,185±595 kcal) in a similar number of training sessions between (60 vs. 59 training sessions) as control during the 26 days leading up to the event. The nature of the training observed in the treatment group would translate to a better race performance according to the literature.

2.2 Protein Biomarkers

When analyzing for protein biomarkers that had at least 1.2 fold change we found groups of protein biomarkers that

were significantly upregulated at PRE (FIG. 8A "Curcumin+Pomegranate+MSM/No Supplement"; Osteonectin/SPARC, sEGFR and sIL-2Rα), 4 H (FIG. 8B "Curcumin+Pomegranate+MSM/No Supplement"; Osteonectin/SPARC, and BDNF), and 24 H (FIG. 8C "Curcumin+Pomegranate+MSM/No Supplement"; Osteonectin/SPARC, and BDNF) compared to control. Numerical changes for all proteins measured are shown in FIG. 9 (row 1 from top, “**” indicates up-regulation: BDNF*, FABP3, Fractalkine, GM-CSF, IFNg, IL-10, IL-12p70; row 2: IL-13, IL-15, IL-17A, IL-1beta, IL-2, IL-23, IL-4; row 3: IL-5, IL-6, IL-7, IL-8, ITAC, MIP-1alpha, MIP-1beta; row 4: MIP-3alpha, Oncostatin M, OSM, Osteonectin SPARC*, sEGFR*, sgp130, sIL-1RI, sIL-1RII; row 5: sIL-2Ralpha*, sIL-4R, sIL-6R, sRAGE, sTNFRI, sTNFRII, sVEGFR1; row 6: sVEGFR2, sVEGFR3, TNF-alpha. Control (light grey) and Treatment (dark grey) are shown for each, left to right, PRE-RACE, 4 H post-race, and 24 H post race.)

2.3 RNA Biomarkers

When analyzing for RNA biomarkers that had at least 1.2 fold change we found groups of biomarkers that were significantly upregulated at PRE (FIG. 10A; PPARg & NOX1) and 24 H (FIG. 10C; PPARg, NOX1, and CCL22) compared to control. No RNA were found to significantly increase relative to control at 4 H (FIG. 10B). We also identified RNA that were significantly downregulated compared to control at PRE (FIG. 10A; PACER, PTGES, MYD88, TNFS14, SOD3, THRIL, and TRAF6), 4 H (FIG. 10B; PTGES, THRIL, MALAT1, PACER, SOD3, SATIII, CX3CL1, LNC00305), and 24 H (FIG. 10C; TRAF6, MYD88, PTGES, and TNFS14). Numerical changes for all RNA measured are shown in FIG. 11 (“**” indicates upregulation, “***” indicates down regulation (FC≥1.2). Row 1 from top: CAT, CCL2, CCL22*, CD40LG, CX3CL1**, CXCL1, GPX1, GUSB; row 2: HPRT1, IL10, IL17A, IL18, IL1B, IL1RN, IL4, IL6; row 3: IL6R, IL7R, IL8, LINC00305**, MALAT1**, MAPK14, MOK, MYD88**; row 4: NEAT1, NFKB1, NKILA, NOX1*, PACER**, PLA2G4A, PPARG*, PPARGC1A; row 5: PPIB, PTGES**, PTGS1, PTGS2, PTPN1, SATIII**, SOD1, SOD2; row 6: SOD3**, THRIL**, TLR2, TLR4, TNF, TNFRSF1A, TNFRSF1B, TNFSF14**; row 7: TRAF6**, VEGFC. Control (light grey) and Treatment (dark grey) are shown for each, left to right, PRE-RACE, 4 H post-race, and 24 H post race.).

3 Discussion

The present study aimed to identify the effect of dietary supplementation with a combination of curcumin, pomegranate, and MSM on inflammation-associated protein and RNA biomarkers prior to and after a half marathon race performance. This study is part of our larger research agenda, which aims to understand and improve biological response to muscle injury and repair. Through this work, our goal is to develop more effective strategies to improve the effectiveness of exercise training, while minimizing common side effects (i.e. soreness, inflammation, overuse injuries, etc.). As the science of biomarker detection has advanced, it has become possible for small labs to expand their measurement capacity with minimal increase in study cost. The present study took advantage of bead-based multiplexing to measure a broad array of inflammation-associated protein and RNA biomarkers. While science has advanced such that multiplexing is within reach for most laboratories, drawing conclusions has become more complicated because new statistical techniques are needed to

develop a treatment response profile. To address this later issue, we used statistical methodology that resulted in the creation of volcano plots at each time point comparing treatment (Restoridyn®+MSM) to control and uniquely identified biomarkers that were either up or down regulated/ expressed with treatment. Distance running is commonly investigated in the scientific literature; however, attempts to minimize side effects with dietary treatments have been inconsistent. The present study demonstrates when strategically used, a combination dietary polyphenol and MSM treatment was associated with reductions in inflammation-associated RNA and an increase in muscle recovery proteins. The present study was focused on short-term recovery (within the 1st 24-h) because this is a critical period of time that affects the ability to return to next practice and activities of daily living.

The observed treatment response profile for protein biomarkers was consistent with an increase in the muscle recovery rate at both 4-h and 24-h (increased Osteonectin/ SPARC, and BDNF). Also, we observed a pre-exercise response profile consistent with an increased ability to control type 1 cytokines (increased sEGFR and sIL-2R α). In the last decade, it was determined that during exercise, skeletal muscle is highly metabolically active and releases a variety of myokines that have systemic implications. According to the literature it is clear when exercise is sustained for long periods of time, myokine release is increased compared to shorter exercise durations. Osteonectin/SPARC and BDNF both play a role in promoting recovery from injury. Thus, based on previous research the treatment response profile resulted in conditions that favored a more rapid return to exercise and normal activities following the half-marathon race.

With respect to RNA biomarkers, the observed treatment response profile included a reduction in inflammation-associated RNA at both 4-h and 24-h with treatment (PACER, PTGES, MYD88, TNFS14, THRIL, TRAF6, CX2CL1, MALAT1, and LNC00305). The treatment response profile also included increase expression of anti-inflammatory RNA (PPAR γ , NOX1, and CCL22). Interestingly, the treatment response profile included reductions in inflammation-associated RNA, but not the corresponding proteins. Our lab and others have demonstrated that controlled, muscle-damaging laboratory exercise can cause transient disruptions in systemic inflammatory proteins. It is possible that the present results differ because the degree of muscle damage was much lower with the half-marathon model than traditional muscle damage models (i.e. eccentric reps, down-hill running, etc.). Given that we observed reductions in inflammation-associated RNA, it is also possible that the treatment delayed the inflammatory protein response until after 24-h post-race. Regardless, the treatment response profile that includes the observed changes in proteins and RNA reflects an improved recovery from running a half-marathon during the early recovery period.

No study is without limitations and the present study is certainly no exception. While we worked very hard to delimit as many variables as possible, when using an applied, field-based study model difficulty are to be expected. One potential limitation of the present study is the small sample size, although this was mitigated by the fact that we used a unique statistical approach that focused on identifying a treatment response profile using all the protein and RNA biomarkers in combination at each time point. This approach was determined a priori to specifically address what we planned to be a small sample size. Another potential limitation of this study is associated with the selected time

points for blood collection. The time points were selected to focus on the early phase of recovery for exercise consistent with what we have previously studied. Given the difference in response between protein and RNA biomarkers during this period, it is reasonable to speculate that additional treatment response profiles may exist for later recovery (>24-h post exercise). Through this process, we identified a unique treatment response profile.

In summary, oral supplementation with combined curcumin, pomegranate, MSM resulted in an improved inflammatory and muscle recovery response during the first 24-h after running a half marathon. Better management of post exercise inflammation may translate to faster, more effective recovery. An applied goal of this work was to determine how to improve the speed of return to normal activities and exercise training. The treatment response profile was determined by combining bead-based measurements with volcano plots to uniquely identify treatment effects using all of the outcome variables in combination. It is noteworthy that these changes were observed in a group of free living adults who did not exercise in the confines of a laboratory, yet we found responses that were very consistent to what our lab and others have observed in laboratory-based models of muscle injury and recovery.

The use of the terms "a," "an," "the," and similar referents in the context of describing the present invention (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. Use of the term "about" is in an embodiment intended to describe values either above or below the stated value in a range of approximately $\pm 10\%$; in other embodiments, the values may range in value above or below the stated value in a range of approximately $\pm 5\%$; in other embodiments, the values may range in value above or below the stated value in a range of approximately $\pm 2\%$; in other embodiments, the values may range in value above or below the stated value in a range of approximately $\pm 1\%$. The preceding ranges are intended to be made clear by context, and no further limitation is implied. All method steps described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise stated. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

While in the foregoing specification the present invention has been described in relation to certain embodiments thereof, and many details have been put forth for the purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that certain of the details described herein can be varied considerably without departing from the basic principles of the invention.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof, and, accordingly, reference should be made to the appended claims, rather than to the foregoing specification, as indicating the scope of the invention.

SUPPLEMENTARY TABLE 1

Summary of Protein biomarkers			
Abbreviation	Name	Type	Relevance
Fractalkine	Fractalkine	Cytokine	Inflammation
GM-CSF	Granulocyte macrophage colony-stimulating factor	Cytokine	Inflammation
IFNg	Interferon-gamma	Cytokine	Inflammation
IL-10	Interleukin-10	Cytokine	Inflammation
IL-12p70	Interleukin-12 (bioactive form)	Cytokine	Inflammation
IL-13	Interleukin-13	Cytokine	Inflammation
IL-17A	Interleukin-17A	Cytokine	Inflammation
IL-1beta	Interleukin-1 beta	Cytokine	Inflammation
IL-2	Interleukin-2	Cytokine	Inflammation
IL-23	Interleukin-23	Cytokine	Inflammation
IL-4	Interleukin-4	Cytokine	Inflammation
IL-5	Interleukin-5	Cytokine	Inflammation
IL-6	Interleukin-6	Cytokine	Inflammation
IL-7	Interleukin-7	Cytokine	Inflammation
IL-8	Interleukin-8	Cytokine	Inflammation
ITAC	Interferon-inducible T cell alpha chemoattractant	Cytokine	Inflammation
MIP-1alpha	C-C motif chemokine 3	Cytokine	Inflammation
MIP-1beta	C-C motif chemokine 4	Cytokine	Inflammation
MIP-3alpha	C-C motif chemokine 20	Cytokine	Inflammation
TNF-alpha	Tumor necrosis factor alpha	Cytokine	Inflammation
IL-15	Interleukin-15	Myokine	Inflammation
Oncostatin M	Oncostatin-M	Myokine	Inflammation
M OSM	Soluble epidermal growth factor receptor	Soluble cytokine receptor	Inflammation
SEGFR	Soluble gp130	Soluble cytokine receptor	Inflammation
SIL-1RI	Soluble interleukin-1 receptor, type 1	Soluble cytokine receptor	Inflammation
SIL-1RII	Soluble interleukin-1 receptor, type 2	Soluble cytokine receptor	Inflammation
SIL-2Ralpha	Soluble interleukin-2 receptor subunit alpha	Soluble cytokine receptor	Inflammation
SIL-4R	Soluble interleukin-4 receptor	Soluble cytokine receptor	Inflammation
SIL-6R	Soluble interleukin-6 receptor	Soluble cytokine receptor	Inflammation
SRAGE	Soluble receptor for advanced glycation end-products	Soluble cytokine receptor	Inflammation
STNFRI	Soluble tumor necrosis factor receptor 1	Soluble cytokine receptor	Inflammation
STNFRII	Soluble tumor necrosis factor receptor 2	Soluble cytokine receptor	Inflammation
SVEGFR1	Soluble vascular endothelial growth factor receptor-1	Soluble cytokine receptor	Inflammation
SVEGFR2	Soluble vascular endothelial growth factor receptor-2	Soluble cytokine receptor	Inflammation
BDNF	Brain-derived neurotrophic factor	Myokine	Muscle injury
FABP3	Fatty acid-binding protein 3	Myokine	Muscle injury
Osteonectin/SPARC	Osteonectin/SPARC	Myokine	Muscle injury
SVEGFR3	Soluble vascular endothelial growth factor receptor-3	Soluble cytokine receptor	Muscle injury

SUPPLEMENTARY TABLE 2

Summary of bead-based RNA biomarkers				
5	Abbreviation	Name	Type	Pathway
	LINC00305	Long Intergenic Non-Protein Coding RNA 305	lncRNA	Inflammation
10	MALAT1	Metastasis associated lung adenocarcinoma transcript 1	lncRNA	Inflammation
	NEAT1	Nuclear paraspeckle assembly transcript 1	lncRNA	Inflammation
15	NKILA	NF-kappaB interacting lncRNA	lncRNA	Inflammation
	PACER	P50-associated COX-2 extragenic RNA	lncRNA	Inflammation
	THRIL	TNF and HNRNPL related immunoregulatory long non-coding RNA	lncRNA	Inflammation
20	CCL2	C-C motif chemokine ligand 2	mRNA	Inflammation
	CCL22	C-C motif chemokine ligand 22	mRNA	Inflammation
	CD40LG	CD40 ligand	mRNA	Inflammation
	CX3CL1	C-X3-C motif chemokine ligand 1	mRNA	Inflammation
25	CXCL1	C-X-C motif chemokine ligand 1	mRNA	Inflammation
	IL10	Interleukin 10	mRNA	Inflammation
	IL17A	Interleukin 17A	mRNA	Inflammation
	IL18	Interleukin 18	mRNA	Inflammation
	IL1B	Interleukin 1 beta	mRNA	Inflammation
30	IL1RN	Interleukin 1 receptor antagonist	mRNA	Inflammation
	IL4	Interleukin 4	mRNA	Inflammation
	IL6	Interleukin 6	mRNA	Inflammation
	IL6R	Interleukin 6 receptor	mRNA	Inflammation
35	IL7R	Interleukin 7 receptor	mRNA	Inflammation
	IL8	Interleukin 8	mRNA	Inflammation
	MOK	MOK protein kinase	mRNA	Inflammation
	MYD88	Innate immune signal transduction adaptor MYD88	mRNA	Inflammation
40	NFKB1	Nuclear factor kappa B subunit 1	mRNA	Inflammation
	PTGES	Prostaglandin E synthase	mRNA	Inflammation
	PTGS1	Prostaglandin-endoperoxide synthase 1	mRNA	Inflammation
45	PTGS2	Prostaglandin-endoperoxide synthase 2	mRNA	Inflammation
	PTPN1	Protein tyrosine phosphatase, non-receptor type 1	mRNA	Inflammation
	SATIII	Satellite III (clone 18)	mRNA	Inflammation
50	TLR2	Toll like receptor 2	mRNA	Inflammation
	TLR4	Toll like receptor 4	mRNA	Inflammation
	TNF	Tumor necrosis factor	mRNA	Inflammation
	TNFRSF1A	TNF receptor superfamily member 1A	mRNA	Inflammation
55	TNFRSF1B	TNF receptor superfamily member 1B	mRNA	Inflammation
	TNFSF14	TNF superfamily member 14	mRNA	Inflammation
	TRAF6	TNF receptor associated factor 6	mRNA	Inflammation
60	VEGFC	Vascular endothelial growth factor C	mRNA	Muscle injury
	GUSB	Glucuronidase beta	mRNA	Housekeeper
	HPRT1	Hypoxanthine phosphoribosyltransferase 1	mRNA	Housekeeper
65	PPIB	Peptidylprolyl isomerase B	mRNA	Housekeeper

SUPPLEMENTARY TABLE 3

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
CD160	CD160 molecule	mRNA	Adaptive Immune System
CD1A	CD1a molecule	mRNA	Adaptive Immune System
CD96	CD96 molecule	mRNA	Adaptive Immune System
ICAM4	intercellular adhesion molecule 4 (Landsteiner-Wiener blood group)	mRNA	Adaptive Immune System
ICAM5	intercellular adhesion molecule 5, telencephalin	mRNA	Adaptive Immune System
KLRF1	killer cell lectin-like receptor subfamily F, member 1	mRNA	Adaptive Immune System
LILRA1	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 1	mRNA	Adaptive Immune System
LILRA2	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 2	mRNA	Adaptive Immune System
LILRA4	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 4	mRNA	Adaptive Immune System
LILRA5	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 5	mRNA	Adaptive Immune System
LILRB4	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 4	mRNA	Adaptive Immune System
LILRB5	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 5	mRNA	Adaptive Immune System
BCL2L11	BCL2-like 11 (apoptosis facilitator)	mRNA	Apoptosis
CD82	CD82 molecule	mRNA	Apoptosis
CRADD	CASP2 and RIPK1 domain containing adaptor with death domain	mRNA	Apoptosis
CUL9	cullin 9	mRNA	Apoptosis
PDCD2	programmed cell death 2	mRNA	Apoptosis
ATG10	ATG10 autophagy related 10 homolog (<i>S. cerevisiae</i>)	mRNA	Autophagy
LILRB3	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 3	mRNA	B cell Receptor Signaling; Adaptive Immune System
CD34	CD34 molecule	mRNA	Cell Adhesion
ITGAE	integrin, alpha E (antigen CD103, human mucosal lymphocyte antigen 1; alpha polypeptide)	mRNA	Cell Adhesion
TGFBI	transforming growth factor, beta-induced, 68 kDa	mRNA	Cell Adhesion
CD22	CD22 molecule	mRNA	Cell Adhesion; B cell Receptor Signaling; Adaptive Immune System
CCBP2	chemokine binding protein 2	mRNA	Chemokine Signaling
CCR1	chemokine (C-C motif) receptor-like 1	mRNA	Chemokine Signaling
CCR2	chemokine (C-C motif) receptor-like 2	mRNA	Chemokine Signaling
CISH	cytokine inducible SH2-containing protein	mRNA	Cytokine Signaling
CSF1R	colony stimulating factor 1 receptor	mRNA	Cytokine Signaling
CSF3R	colony stimulating factor 3 receptor (granulocyte)	mRNA	Cytokine Signaling
IL11RA	interleukin 11 receptor, alpha	mRNA	Cytokine Signaling
IL13RA1	interleukin 13 receptor, alpha 1	mRNA	Cytokine Signaling
IL16	interleukin 16	mRNA	Cytokine Signaling
IL17B	interleukin 17B	mRNA	Cytokine Signaling
IL19	interleukin 19	mRNA	Cytokine Signaling

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
IL1RL1	interleukin 1 receptor-like 1	mRNA	Cytokine Signaling
IL1RN	interleukin 1 receptor antagonist	mRNA	Cytokine Signaling
IL20	interleukin 20	mRNA	Cytokine Signaling
IL22RA2	interleukin 22 receptor, alpha 2	mRNA	Cytokine Signaling
IL26	interleukin 26	mRNA	Cytokine Signaling
IL32	interleukin 32	mRNA	Cytokine Signaling
IL9	interleukin 9	mRNA	Cytokine Signaling
S1PR1	sphingosine-1-phosphate receptor 1	mRNA	Cytokine Signaling
TNFRSF17	tumor necrosis factor receptor superfamily, member 17	mRNA	Cytokine Signaling
TNFRSF8	tumor necrosis factor receptor superfamily, member 8	mRNA	Cytokine Signaling
TNFSF12	tumor necrosis factor (ligand) superfamily, member 12	mRNA	Cytokine Signaling
TNFSF15	tumor necrosis factor (ligand) superfamily, member 15	mRNA	Cytokine Signaling
CCL11	chemokine (C-C motif) ligand 11	mRNA	Cytokine Signaling; Chemokine
CCL15	chemokine (C-C motif) ligand 15	mRNA	Cytokine Signaling; Chemokine
CCL16	chemokine (C-C motif) ligand 16	mRNA	Cytokine Signaling; Chemokine
CCL18	chemokine (C-C motif) ligand 18 (pulmonary and activation- regulated)	mRNA	Cytokine Signaling; Chemokine
CCL22	chemokine (C-C motif) ligand 22	mRNA	Cytokine Signaling; Chemokine
CCL23	chemokine (C-C motif) ligand 23	mRNA	Cytokine Signaling; Chemokine
CCL24	chemokine (C-C motif) ligand 24	mRNA	Cytokine Signaling; Chemokine
CCL26	chemokine (C-C motif) ligand 26	mRNA	Cytokine Signaling; Chemokine
CCL7	chemokine (C-C motif) ligand 7	mRNA	Cytokine Signaling; Chemokine
CCL8	chemokine (C-C motif) ligand 8	mRNA	Cytokine Signaling; Chemokine
CCR1	chemokine (C-C motif) receptor 1	mRNA	Cytokine Signaling; Chemokine
CCR10	chemokine (C-C motif) receptor 10	mRNA	Cytokine Signaling; Chemokine
CCR8	chemokine (C-C motif) receptor 8	mRNA	Cytokine Signaling; Chemokine
CX3CR1	chemokine (C-X3-C motif) receptor 1	mRNA	Cytokine Signaling; Chemokine
CXCL13	chemokine (C-X-C motif) ligand 13	mRNA	Cytokine Signaling; Chemokine
CXCR3	chemokine (C-X-C motif) receptor 3	mRNA	Cytokine Signaling; Chemokine
CXCR6	chemokine (C-X-C motif) receptor 6	mRNA	Cytokine Signaling; Chemokine

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
XCR1	chemokine (C motif) receptor 1	mRNA	Cytokine Signaling; Chemokine Signaling
CD9	CD9 molecule	mRNA	Hemostasis
EDNRB	endothelin receptor type B	mRNA	Hemostasis
FCGR1T	Fc fragment of IgG, receptor, transporter, alpha	mRNA	Hemostasis
GP1BB	glycoprotein Ib (platelet), beta polypeptide	mRNA	Hemostasis
HAMP	hepcidin antimicrobial peptide	mRNA	Hemostasis
CSF2RB	colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)	mRNA	Hemostasis; Cytokine Signaling; Apoptosis
IL3	interleukin 3 (colony-stimulating factor, multiple)	mRNA	Hemostasis; Cytokine Signaling; Apoptosis
C14orf166	chromosome 14 open reading frame 166	mRNA	Host-pathogen Interaction
CD3EAP	CD3e molecule, epsilon associated protein	mRNA	Host-pathogen Interaction
IRGM	immunity-related GTPase family, M	mRNA	Host-pathogen Interaction
KLRB1	Killer cell lectin-like receptor subfamily B, member I	mRNA	Host-pathogen Interaction; Adaptive immune System
MASP2	Mannan-binding lectin serine peptidase 2	mRNA	Host-pathogen Interaction; Complement System
IL1A	Interleukin 1, alpha	mRNA	Host-pathogen Interaction; Cytokine Signaling
IL1R2	Interleukin 1 receptor, type II	mRNA	Host-pathogen Interaction; Cytokine Signaling
CCR5	Chemokine (C-C motif) receptor 5	mRNA	Host-pathogen Interaction; Cytokine Signaling; Chemokine Signaling
ITGA2B	Integrin, alpha 2b (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41)	mRNA	Host-pathogen Interaction; Hemostasis
ITGA6	Integrin, alpha 6	mRNA	Host-pathogen Interaction; Hemostasis; Cell Adhesion
SEPLG	Selectin P ligand	mRNA	Host-pathogen Interaction; Hemostasis; Cell Adhesion
C1QBP	Complement component 1, q subcomponent binding protein	mRNA	Host-pathogen Interaction; Hemostasis; Complement System
PDGFB	Platelet-derived growth factor beta polypeptide	mRNA	Host-pathogen Interaction; Hemostasis; Cytokine Signaling
ABCF1	ATP-binding cassette, sub-family F (GCN20), member 1	mRNA	Housekeeper
ALAS1	Aminolevulinate, delta-,synthase 1	mRNA	Housekeeper
EEF1G	Eukaryotic translation elongation factor 1 gamma	mRNA	Housekeeper
G6PD	Glucose-6-phosphate dehydrogenase	mRNA	Housekeeper
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	mRNA	Housekeeper

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
GUSB	Glucuronidase, beta	mRNA	Housekeeper
HPRT1	Hypoxanthine phosphoribosyltransferase 1	mRNA	Housekeeper
OAZ1	Ornithine decarboxylase antizyme 1	mRNA	Housekeeper
POLR1B	Polymerase (RNA) I polypeptide B, 128 kDa	mRNA	Housekeeper
POLR2A	Polymerase (RNA) II (DNA directed) polypeptide A, 220 kDa	mRNA	Housekeeper
PPIA	Peptidylprolyl isomerase A (cyclophilin A)	mRNA	Housekeeper
RPL19	Ribosomal protein L19	mRNA	Housekeeper
SDHA	Succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	mRNA	Housekeeper
TBP	TATA box binding protein	mRNA	Housekeeper
TUBB	Tubulin, beta	mRNA	Housekeeper
KLRAP1	Killer cell lectin-like receptor subfamily A pseudogene 1	mRNA	Immune System
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1	mRNA	Immunometabolism
B3GAT1	Beta-1,3-glucuronyltransferase 1 (glucuronosyltransferase P)	mRNA	Immunometabolism
CMKLR1	Chemokine-like receptor 1	mRNA	Immunometabolism
FKBP5	FK506 binding protein 5	mRNA	Immunometabolism
KCNJ2	Potassium inwardly-rectifying channel, subfamily J, member 2	mRNA	Immunometabolism
LTB4R	Leukotriene B4 receptor	mRNA	Immunometabolism
LTB4R2	Leukotriene B4 receptor 2	mRNA	Immunometabolism
NTSE	5'-nucleotidase, ecto (CD73)	mRNA	Immunometabolism
PLA2G2E	Phospholipase A2, group IIE	mRNA	Immunometabolism
RARRES3	Retinoic acid receptor responder (tazarotene induced) 3	mRNA	Immunometabolism
ARG2	Arginase, type II	mRNA	Immunometabolism; Host-pathogen interaction
ENTPD1	Ectonucleoside triphosphate diphosphohydrolase 1	mRNA	Immunometabolism; Host-pathogen interaction
SLC2A1	Solute carrier family 2 (facilitated glucose transporter), member 1	mRNA	Immunometabolism; Host-pathogen interaction
CD53	CD53 molecule	mRNA	Innate Immune System
CD97	CD97 molecule	mRNA	Innate Immune System
CLEC4A	C-type lectin domain family 4, member A	mRNA	Innate Immune System
CLEC5A	C-type lectin domain family 5, member A	mRNA	Innate Immune System
CLEC6A	C-type lectin domain family 6, member A	mRNA	Innate Immune System
DEFB1	Defensin, beta 1	mRNA	Innate Immune System
DEFB103A	Defensin, beta 103A	mRNA	Innate Immune System
DEFB103B	Defensin, beta 103B	mRNA	Innate Immune System
DEFB4A	Defensin, beta 4A	mRNA	Innate Immune System
FCER1A	Fc fragment of IgE, high affinity 1, receptor for; alpha polypeptide	mRNA	Innate Immune System
GNLY	Granulysin	mRNA	Innate Immune System
ITLN1	Intelectin 1	mRNA	Innate Immune System
ITLN2	Intelectin 2	mRNA	Innate Immune System
LTF	Lactotransferrin	mRNA	Innate Immune System
MME	Membrane metallo-endopeptidase	mRNA	Innate Immune System
PIGR	polymeric immunoglobulin receptor	mRNA	Innate Immune System
TNFAIP6	tumor necrosis factor, alpha-induced protein 6	mRNA	Innate Immune System

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
LAIR1	leukocyte-associated immunoglobulin-like receptor 1	mRNA	Innate Immune System; Adaptive Immune System
LILRA3	leukocyte immunoglobulin-like receptor, subfamily A (without TM domain), member 3	mRNA	Innate Immune System; Adaptive Immune System
ICAM3	intercellular adhesion molecule 3	mRNA	Innate Immune System; Cell Adhesion; Adaptive Immune System
C6	complement component 6	mRNA	Innate Immune System; Complement System
C7	complement component 7	mRNA	Innate Immune System; Complement System
MUC1	mucin 1, cell surface associated	mRNA	Innate Immune System; Cytokine Signaling
CCR6	chemokine (C-C motif) receptor 6	mRNA	Innate Immune System; Cytokine Signaling; Chemokine Signaling
CXCR1	chemokine (C-X-C motif) receptor 1	mRNA	Innate Immune System; Cytokine Signaling; Chemokine Signaling
CXCR2	chemokine (C-X-C motif) receptor 2	mRNA	Innate Immune System; Cytokine Signaling; Chemokine Signaling
CEACAM6	carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen)	mRNA	Innate Immune System; Hemostasis
CEACAM8	carcinoembryonic antigen-related cell adhesion molecule 8	mRNA	Innate Immune System; Hemostasis
SELL	selectin L	mRNA	Innate Immune System; Hemostasis; Cell Adhesion; Adaptive Immune System
CLU	clusterin	mRNA	Innate Immune System; Hemostasis; Complement System
PLAUR	plasminogen activator, urokinase receptor	mRNA	Innate Immune System; Hemostasis; Complement System
PPBP	pro-platelet basic protein (chemokine (C-X-C motif) ligand 7)	mRNA	Innate Immune System; Hemostasis; Cytokine Signaling; Chemokine Signaling
IFIH1	interferon induced with helicase C domain 1	mRNA	Innate Immune System; Host-pathogen Interaction
C1QA	complement component 1, q subcomponent, A chain	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
C1QB	complement component 1, q subcomponent, B chain	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
C1S	complement component 1, s subcomponent	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
C2	complement component 2	mRNA	Innate Immune System; Host-pathogen

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
C4A/B	complement component 4A (Rodgers blood group)/complement component 4B (Chido blood group)	mRNA	Interaction; Complement System Innate Immune System; Host-pathogen
C4BPA	complement component 4 binding protein, alpha	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
C5	complement component 5	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
C8A	complement component 8, alpha polypeptide	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
C8B	complement component 8, beta polypeptide	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
C8G	complement component 8, gamma polypeptide	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
C9	complement component 9	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
CFB	complement factor B	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
CFH	complement factor H	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
CFI	complement factor I	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
CFP	complement factor properdin	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
CR1	complement component (3b/4b) receptor 1 (Knops blood group)	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
MASP1	mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive factor)	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
VTN	vitronectin	mRNA	Innate Immune System; Host-pathogen Interaction; Complement System
CD19	CD19 molecule	mRNA	Innate Immune System; Host-pathogen Interaction; Complement

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
CD58	CD58 molecule	mRNA	System; B cell Receptor Signaling; Adaptive Immune System Innate Immune System; Host-pathogen Interaction; Hemostasis; Cell Adhesion
CFD	complement factor D (adipsin)	mRNA	Innate Immune System; Host-pathogen Interaction; Hemostasis; Complement System
SERPING1	serpin peptidase inhibitor, clade G (C1 inhibitor), member 1	mRNA	Innate Immune System; Host-pathogen Interaction; Hemostasis; Complement System
NOS2	nitric oxide synthase 2, inducible	mRNA	Innate Immune System; Host-pathogen Interaction; Hemostasis; Cytokine Signaling
ITGAX	integrin, alpha X (complement component 3 receptor 4 subunit)	mRNA	Innate Immune System; Host-pathogen Interaction; Hemostasis; Cytokine Signaling; Complement System; Cell Adhesion
GPI	glucose-6-phosphate isomerase	mRNA	Innate Immune System; Immunometabolism
PLA2G2A	phospholipase A2, group II A (platelets, synovial fluid)	mRNA	Innate Immune System; Immunometabolism
AICDA	activation-induced cytidine deaminase	mRNA	Lymphocyte Activation
AIRE	autoimmune regulator	mRNA	Lymphocyte Activation
CD24	CD24 molecule	mRNA	Lymphocyte Activation
CD5	CD5 molecule	mRNA	Lymphocyte Activation
CD7	CD7 molecule	mRNA	Lymphocyte Activation
CD83	CD83 molecule	mRNA	Lymphocyte Activation
DPP4	dipeptidyl-peptidase 4	mRNA	Lymphocyte Activation
GPR183	G protein-coupled receptor 183	mRNA	Lymphocyte Activation
HFE	hemochromatosis	mRNA	Lymphocyte Activation
KLRC3	killer cell lectin-like receptor subfamily C, member 3	mRNA	Lymphocyte Activation
KLRC4	killer cell lectin-like receptor subfamily C, member 4	mRNA	Lymphocyte Activation
KLRF2	killer cell lectin-like receptor subfamily F, member 2	mRNA	Lymphocyte Activation
KLRG2	killer cell lectin-like receptor subfamily G, member 2	mRNA	Lymphocyte Activation
LILRB2	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 2	mRNA	Lymphocyte Activation
MS4A1	membrane-spanning 4-domains, subfamily A, member 1	mRNA	Lymphocyte Activation
PRDM1	PR domain containing 1, with ZNF domain	mRNA	Lymphocyte Activation
BTLA	B and T lymphocyte associated	mRNA	Lymphocyte Activation; Adaptive

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
KIR_Inhibiting_Sub_group_1	killer cell immunoglobulin-like receptor	mRNA	Immune System Lymphocyte Activation; Adaptive Immune System
KIR_Inhibiting_Sub_group_2	killer cell immunoglobulin-like receptor	mRNA	Immune System Lymphocyte Activation; Adaptive Immune System
KIR3DL1	killer cell immunoglobulin-like receptor, three domains, long cytoplasmic tail, 1	mRNA	Lymphocyte Activation; Adaptive Immune System
KIR3DL2	killer cell immunoglobulin-like receptor, three domains, long cytoplasmic tail, 2	mRNA	Lymphocyte Activation; Adaptive Immune System
KIR3DL3	killer cell immunoglobulin-like receptor, three domains, long cytoplasmic tail, 3	mRNA	Lymphocyte Activation; Adaptive Immune System
KLRC1	killer cell lectin-like receptor subfamily C, member 1	mRNA	Lymphocyte Activation; Adaptive Immune System
KLRG1	killer cell lectin-like receptor subfamily G, member 1	mRNA	Lymphocyte Activation; Adaptive Immune System
LILRB1	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 1	mRNA	Lymphocyte Activation; Adaptive Immune System
NCR1	natural cytotoxicity triggering receptor 1	mRNA	Lymphocyte Activation; Adaptive Immune System
SLAMF6	SLAM family member 6	mRNA	Lymphocyte Activation; Adaptive Immune System
SLAMF7	SLAM family member 7	mRNA	Lymphocyte Activation; Adaptive Immune System
GZMA	granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3)	mRNA	Lymphocyte Activation; Apoptosis
GZMB	granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1)	mRNA	Lymphocyte Activation; Apoptosis
GZMK	granzyme K (granzyme 3; tryptase II)	mRNA	Lymphocyte Activation; Apoptosis
PRF1	perforin 1 (pore forming protein)	mRNA	Lymphocyte Activation; Apoptosis
CD79A	CD79a molecule, immunoglobulin-associated alpha	mRNA	Lymphocyte Activation; B cell Receptor Signaling; Adaptive Immune System
CD79B	CD79b molecule, immunoglobulin-associated beta	mRNA	Lymphocyte Activation; B cell Receptor Signaling; Adaptive Immune System
CD276	CD276 molecule	mRNA	Lymphocyte Activation; Cell Adhesion
CD6	CD6 molecule	mRNA	Lymphocyte Activation; Cell Adhesion
TIGIT	T cell immunoreceptor with Ig and ITIM domains	mRNA	Lymphocyte Activation; Cell Adhesion

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
CD274	CD274 molecule	mRNA	Lymphocyte Activation; Cell Adhesion; Adaptive Immune System
ICOSLG	inducible T-cell co-stimulator ligand	mRNA	Lymphocyte Activation; Cell Adhesion; Adaptive Immune System
PDCD1LG2	programmed cell death 1 ligand 2	mRNA	Lymphocyte Activation; Cell Adhesion; Adaptive Immune System
BCL6	B-cell CLL/lymphoma 6	mRNA	Lymphocyte Activation; Cytokine Signaling
CD27	CD27 molecule	mRNA	Lymphocyte Activation; Cytokine Signaling
CD70	CD70 molecule	mRNA	Lymphocyte Activation; Cytokine Signaling
EBI3	Epstein-Barr virus induced 3	mRNA	Lymphocyte Activation; Cytokine Signaling
HAVCR2	hepatitis A virus cellular receptor 2	mRNA	Lymphocyte Activation; Cytokine Signaling
IL1RL2	interleukin 1 receptor-like 2	mRNA	Lymphocyte Activation; Cytokine Signaling
IL27	interleukin 27	mRNA	Lymphocyte Activation; Cytokine Signaling
IL28A	interleukin 28A (interferon, lambda 2)	mRNA	Lymphocyte Activation; Cytokine Signaling
IL28A/B	interleukin 28A (interferon, lambda 2)/interleukin 28B (interferon, lambda 3)	mRNA	Lymphocyte Activation; Cytokine Signaling
IL29	interleukin 29 (interferon, lambda 1)	mRNA	Lymphocyte Activation; Cytokine Signaling
IL7	interleukin 7	mRNA	Lymphocyte Activation; Cytokine Signaling
IL7R	interleukin 7 receptor	mRNA	Lymphocyte Activation; Cytokine Signaling
KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	mRNA	Lymphocyte Activation; Cytokine Signaling
PTPN2	protein tyrosine phosphatase, non- receptor type 2	mRNA	Lymphocyte Activation; Cytokine Signaling
RAG1	recombination activating gene 1	mRNA	Lymphocyte Activation; Cytokine Signaling
RAG2	recombination activating gene 2	mRNA	Lymphocyte Activation; Cytokine Signaling
TNFRSF13B	tumor necrosis factor receptor superfamily, member 13B	mRNA	Lymphocyte Activation; Cytokine Signaling
TNFRSF4	tumor necrosis factor receptor superfamily, member 4	mRNA	Lymphocyte Activation; Cytokine Signaling
TNFRSF9	tumor necrosis factor receptor superfamily, member 9	mRNA	Lymphocyte Activation; Cytokine Signaling
TNFSF4	tumor necrosis factor (ligand) superfamily, member 4	mRNA	Lymphocyte Activation; Cytokine Signaling
TNFSF8	tumor necrosis factor (ligand) superfamily, member 8	mRNA	Lymphocyte Activation; Cytokine Signaling

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
XCL1	chemokine (C motif) ligand 1	mRNA	Lymphocyte Activation; Cytokine Signaling; Chemokine Signaling
CD244	CD244 molecule, natural killer cell receptor 2B4	mRNA	Lymphocyte Activation; Hemostasis
CD48	CD48 molecule	mRNA	Lymphocyte Activation; Hemostasis
CD2	CD2 molecule	mRNA	Lymphocyte Activation; Hemostasis; Cell Adhesion
KLRK1	killer cell lectin-like receptor subfamily K, member 1	mRNA	Lymphocyte Activation; Host-pathogen Interaction
PTGER4	prostaglandin E receptor 4 (subtype EP4)	mRNA	Lymphocyte Activation; Host-pathogen Interaction
SLAMF1	signaling lymphocytic activation molecule family member 1	mRNA	Lymphocyte Activation; Host-pathogen Interaction
CD1D	CD1d molecule	mRNA	Lymphocyte Activation; Host-pathogen Interaction; Adaptive Immune System
SH2D1A	SH2 domain containing 1A	mRNA	Lymphocyte Activation; Host-pathogen Interaction; Adaptive Immune System
BAX	BCL2-associated X protein	mRNA	Lymphocyte Activation; Host-pathogen Interaction; Apoptosis
BID	BH3 interacting domain death agonist	mRNA	Lymphocyte Activation; Host-pathogen Interaction; Apoptosis
CCND3	cyclin D3	mRNA	Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling
CDKN1A	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	mRNA	Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling
TNFRSF14	tumor necrosis factor receptor superfamily, member 14	mRNA	Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Adaptive Immune System
TNFRSF10C	tumor necrosis factor receptor superfamily, member 10c, decoy without an intracellular domain	mRNA	Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Apoptosis
IDO1	indoleamine 2,3-dioxygenase 1	mRNA	Lymphocyte Activation; Immuno-metabolism; Host-pathogen Interaction
KIR_Activating_Sub_group_1	killer cell immunoglobulin-like receptor	mRNA	Lymphocyte Activation; Innate Immune System
KLRC2	killer cell lectin-like receptor subfamily C, member 2	mRNA	Lymphocyte Activation; Innate Immune System
LGALS3	lectin, galactoside-binding, soluble, 3	mRNA	Lymphocyte Activation; Innate Immune System

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
KIR_Activating_Sub_group_2	killer cell immunoglobulin-like receptor	mRNA	Lymphocyte Activation; Innate Immune System; Adaptive Immune System
KLRD1	killer cell lectin-like receptor subfamily D, member 1	mRNA	Lymphocyte Activation; Innate Immune System; Adaptive Immune System
ICAM2	intercellular adhesion molecule 2	mRNA	Lymphocyte Activation; Innate Immune System; Cell Adhesion; Adaptive Immune System
CD55	CD55 molecule, decay accelerating factor for complement (Cromer blood group)	mRNA	Lymphocyte Activation; Innate Immune System; Complement System
CD59	CD59 molecule, complement regulatory protein	mRNA	Lymphocyte Activation; Innate Immune System; Complement System
CCR2	chemokine (C-C motif) receptor 2	mRNA	Lymphocyte Activation; Innate Immune System; Cytokine Signaling; Chemo kine Signaling
CEACAM1	carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)	mRNA	Lymphocyte Activation; Innate Immune System; Hemostasis
MIF	macrophage migration inhibitory factor (glycosylation-inhibiting factor)	mRNA	Lymphocyte Activation; Innate Immune System; Hemostasis; Cytokine Signaling
CLEC4E	C-type lectin domain family 4, member E	mRNA	Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction
CD46	CD46 molecule, complement regulatory protein	mRNA	Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Complement System
CR2	complement component (3d/Epstein Barr virus) receptor 2	mRNA	Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Complement System; B cell Receptor Signaling
CD81	CD81 molecule	mRNA	Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Complement System; B cell Receptor Signaling; Adaptive Immune System

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
FCER1G	Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide	mRNA	Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Hemostasis
BST1	bone marrow stromal cell antigen 1	mRNA	Lymphocyte Activation; Innate Immune System; Immuno-metabolism
MBP	myelin basic protein	mRNA	Lymphocyte Trafficking
ARHGDIβ	Rho GDP dissociation inhibitor (GDI) beta	mRNA	Lymphocyte Trafficking; Apoptosis
CDH5	cadherin 5, type 2 (vascular endothelium)	mRNA	Lymphocyte Trafficking; Cell Adhesion
CXCR4	chemokine (C-X-C motif) receptor 4	mRNA	Lymphocyte Trafficking; Cytokine Signaling; Chemokine Signaling
CD99	CD99 molecule	mRNA	Lymphocyte Trafficking; Hemostasis; Cell Adhesion; Adaptive Immune System
PECAM1	platelet/endothelial cell adhesion molecule	mRNA	Lymphocyte Trafficking; Innate Immune System; Host-pathogen Interaction; Hemostasis; Cell Adhesion
PTK2	PTK2 protein tyrosine kinase 2	mRNA	Lymphocyte Trafficking; Innate Immune System; Host-pathogen Interaction; Hemostasis; Chemokine Signaling; Apoptosis
THY1	Thy-1 cell surface antigen	mRNA	Lymphocyte Trafficking; Lymphocyte Activation
ITGA4	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	mRNA	Lymphocyte Trafficking; Lymphocyte Activation; Host-pathogen Interaction; Hemostasis; Cell Adhesion; Adaptive Immune System
CTNNB1	catenin (cadherin-associated protein), beta 1, 88 kDa	mRNA	Lymphocyte Trafficking; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction
ITGAL	integrin, alpha L (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide)	mRNA	Lymphocyte Trafficking; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Hemostasis; Cell Adhesion; Adaptive Immune System
MRI	major histocompatibility complex, class I-related	mRNA	MHC Class I Antigen Presentation

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
LILRA6	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 6	mRNA	MHC Class I Antigen Presentation; Adaptive Immune System
TAPBP	TAP binding protein (tapasin)	mRNA	MHC Class I Antigen Presentation; Adaptive Immune System
UBE2L3	ubiquitin-conjugating enzyme E2L3	mRNA	MHC Class I Antigen Presentation; Adaptive Immune System
BCAP31	B-cell receptor-associated protein 31	mRNA	MHC Class I Antigen Presentation; Host-pathogen Interaction; Apoptosis; Adaptive Immune System
ATG7	ATG7 autophagy related 7 homolog (<i>S. cerevisiae</i>)	mRNA	MHC Class I Antigen Presentation; Innate Immune System; Autophagy; Adaptive Immune System
ZBTB16	zinc finger and BTB domain containing 16	mRNA	MHC Class I Antigen Presentation; Lymphocyte Activation; Adaptive Immune System
LAG3	lymphocyte-activation gene 3	mRNA	MHC Class II Antigen Presentation; Lymphocyte Activation; Adaptive Immune System
CD74	CD74 molecule, major histocompatibility complex, class II invariant chain	mRNA	MHC Class II Antigen Presentation; Lymphocyte Activation; Host-pathogen Interaction; Hemostasis; Adaptive Immune System
IKBKAP	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein	mRNA	NF- κ B Signaling
TAGAP	T-cell activation RhoGTPase activating protein	mRNA	NF- κ B Signaling
TNFRSF11A	tumor necrosis factor receptor superfamily, member 11a, NFKB activator	mRNA	NF- κ B Signaling; Cytokine Signaling
CCL13	chemokine (C-C motif) ligand 13	mRNA	NF- κ B Signaling; Cytokine Signaling; Chemokine Signaling
LTBR	lymphotoxin beta receptor (TNFR superfamily, member 3)	mRNA	NF- κ B Signaling; Host-pathogen Interaction; Cytokine Signaling
PLAU	plasminogen activator, urokinase	mRNA	NF- κ B Signaling; Innate Immune System; Hemostasis; Complement System
TNFSF11	tumor necrosis factor (ligand) superfamily, member 11	mRNA	NF- κ B Signaling; Lymphocyte Activation; Cytokine Signaling
TNFSF13B	tumor necrosis factor (ligand) superfamily, member 13b	mRNA	NF- κ B Signaling; Lymphocyte Activation; Cytokine Signaling

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
BLNK	B-cell linker	mRNA	NF-kB Signaling; Lymphocyte Activation; Cytokine Signaling; B cell Receptor Signaling; Adaptive Immune System
ATM	ataxia telangiectasia mutated	mRNA	NF-kB Signaling; Lymphocyte Activation; Host-pathogen Interaction; Apoptosis
TNFRSF13C	tumor necrosis factor receptor superfamily, member 13C	mRNA	NF-kB Signaling; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling
SYK	spleen tyrosine kinase	mRNA	NF-kB Signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Hemostasis; Cytokine Signaling; B cell Receptor Signaling; Adaptive Immune System
CXCL12	chemokine (C-X-C motif) ligand 12	mRNA	NF-kB Signaling; Lymphocyte Trafficking; Cytokine Signaling; Chemokine Signaling
ATG16L1	ATG16 autophagy related 16-like 1 (<i>S. cerevisiae</i>)	mRNA	NLR signaling; Autophagy
IFI16	interferon, gamma-inducible protein 16	mRNA	NLR signaling; Innate Immune System
CASP2	caspase 2, apoptosis-related cysteine peptidase	mRNA	NLR signaling; Innate Immune System; Apoptosis
ATG12	ATG12 autophagy related 12 homolog (<i>S. cerevisiae</i>)	mRNA	NLR signaling; Innate Immune System; Autophagy
CAMP	cathelicidin antimicrobial peptide	mRNA	NLR signaling; Innate Immune System; Host-pathogen Interaction
CARD9	caspase recruitment domain family, member 9	mRNA	NLR signaling; Innate Immune System; Host-pathogen Interaction
TMEM173	transmembrane protein 173	mRNA	NLR signaling; Innate Immune System; Host-pathogen Interaction
CASP1	caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)	mRNA	NLR signaling; Innate Immune System; Inflammasomes; Host-pathogen Interaction; Cytokine Signaling

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers				
Abbreviation	Name	Type	Relevance	
IL18	interleukin 18 (interferon-gamma-inducing factor)	mRNA	NLR signaling; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling	
ATG5	ATG5 autophagy related 5 homolog (<i>S. cerevisiae</i>)	mRNA	NLR signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Autophagy	
NLRP3	NLR family, pyrin domain containing 3	mRNA	NLR signaling; Lymphocyte Activation; Innate Immune System; Inflammasomes; Host-pathogen Interaction	
PYCARD	PYD and CARD domain containing	mRNA	NLR signaling; Lymphocyte Activation; Innate Immune System; Inflammasomes; Host-pathogen Interaction	
IL18RAP	interleukin 18 receptor accessory protein	mRNA	Oxidative Stress; Cytokine Signaling	
MCL1	myeloid cell leukemia sequence 1 (BCL2-related)	mRNA	Oxidative Stress; Cytokine Signaling; Apoptosis	
PDGFRB	platelet-derived growth factor receptor, beta polypeptide	mRNA	Oxidative Stress; Host-pathogen Interaction; Cytokine Signaling	
FN1	fibronectin 1	mRNA	Oxidative Stress; Host-pathogen Interaction; Hemostasis; Cytokine Signaling	
ARG1	arginase, liver	mRNA	Oxidative Stress; Innate Immune System; Immuno-metabolism; Host-pathogen Interaction	
CCR7	chemokine (C-C motif) receptor 7	mRNA	Oxidative Stress; Lymphocyte Activation; Cytokine Signaling; Chemokine Signaling	
SRC	v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)	mRNA	Oxidative Stress; Lymphocyte Activation; Host-pathogen Interaction; Chemokine Signaling	
ADA	adenosine deaminase	mRNA	Oxidative Stress; Lymphocyte Activation; Immuno-metabolism	
ABL1	c-abl oncogene 1, non-receptor tyrosine kinase	mRNA	Oxidative Stress; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Hemostasis	

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
CCL19	chemokine (C-C motif) ligand 19	mRNA	Oxidative Stress; NF- κ B Signaling; Lymphocyte Activation; Cytokine Signaling; Chemokine Signaling
BCL2	B-cell CLL/lymphoma 2	mRNA	Oxidative Stress; NLR signaling; NF- κ B Signaling; Lymphocyte Activation; Innate Immune System; Inflammasomes; Host-pathogen Interaction; Cytokine Signaling; Autophagy; Apoptosis
CD163	CD163 molecule	mRNA	Phagocytosis and Degradation
CD164	CD164 molecule, sialomucin	mRNA	Phagocytosis and Degradation
LAMP3	lysosomal-associated membrane protein 3	mRNA	Phagocytosis and Degradation
LITAF	lipopolysaccharide-induced TNF factor	mRNA	Phagocytosis and Degradation
MARCO	macrophage receptor with collagenous structure	mRNA	Phagocytosis and Degradation
MSR1	macrophage scavenger receptor 1	mRNA	Phagocytosis and Degradation
TFRC	transferrin receptor (p90, CD71)	mRNA	Phagocytosis and Degradation
FCGR2A/C	Fc fragment of IgG, low affinity IIa, receptor (CD32)/Fc fragment of IgG, low affinity IIc, receptor for (CD32)	mRNA	Phagocytosis and Degradation; Host-pathogen Interaction
FCGR2B	Fc fragment of IgG, low affinity IIb, receptor (CD32)	mRNA	Phagocytosis and Degradation; Host-pathogen Interaction; B cell Receptor Signaling; Adaptive Immune System
ITGA5	integrin, alpha 5 (fibronectin receptor, alpha polypeptide)	mRNA	Phagocytosis and Degradation; Host-pathogen Interaction; Hemostasis
IGF2R	insulin-like growth factor 2 receptor	mRNA	Phagocytosis and Degradation; Innate Immune System
CTSG	cathepsin G	mRNA	Phagocytosis and Degradation; Innate Immune System; Host-pathogen Interaction
FCAR	Fc fragment of IgA, receptor for	mRNA	Phagocytosis and Degradation; Innate Immune System; Host-pathogen Interaction
FCGR2A	Fc fragment of IgG, low affinity IIa, receptor (CD32)	mRNA	Phagocytosis and Degradation; Innate Immune System; Host-pathogen Interaction
C1R	complement component 1, r subcomponent	mRNA	Phagocytosis and Degradation; Innate Immune System; Host-pathogen Interaction; Complement System

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
C3	complement component 3	mRNA	Phagocytosis and Degradation; Innate Immune System; Host-pathogen Interaction; Complement System; Adaptive Immune System
CLEC7A	C-type lectin domain family 7, member A	mRNA	Phagocytosis and Degradation; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction
FCGR3A/B	Fc fragment of IgG, low affinity IIIa, receptor (CD16a)/Fc fragment of IgG, low affinity IIIb, receptor (CD16a)	mRNA	Phagocytosis and Degradation; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction
CD209	CD209 molecule	mRNA	Phagocytosis and Degradation; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Adaptive Immune System
ITGB1	integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12)	mRNA	Phagocytosis and Degradation; Lymphocyte Trafficking; Lymphocyte Activation; Host-pathogen Interaction; Hemostasis; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
MRC1	mannose receptor, C type 1	mRNA	Phagocytosis and Degradation; MHC Class I Antigen Presentation; Host-pathogen Interaction; Adaptive Immune System
TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	mRNA	Phagocytosis and Degradation; MHC Class I Antigen Presentation; Host-pathogen Interaction; Adaptive Immune System
TAP2	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	mRNA	Phagocytosis and Degradation; MHC Class I Antigen Presentation; Host-pathogen Interaction; Adaptive Immune System
NCF4	neutrophil cytosolic factor 4, 40 kDa	mRNA	Phagocytosis and Degradation; MHC Class I Antigen Presentation; Lymphocyte Trafficking; Innate Immune System; Host-pathogen Interaction; Adaptive Immune System

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
HLA-DMA	major histocompatibility complex, class II, DM alpha	mRNA	Phagocytosis and Degradation; MHC Class II Antigen Presentation; Host-pathogen Interaction; Cell Adhesion
HLA-DOB	major histocompatibility complex, class II, DO beta	mRNA	Phagocytosis and Degradation; MHC Class II Antigen Presentation; Host-pathogen Interaction; Cell Adhesion; Adaptive Immune System
CTSC	cathepsin C	mRNA	Phagocytosis and Degradation; MHC Class II Antigen Presentation; Innate Immune System; Apoptosis; Adaptive Immune System
HLA-DMB	major histocompatibility complex, class II, DM beta	mRNA	Phagocytosis and Degradation; MHC Class II Antigen Presentation; Lymphocyte Activation; Host-pathogen Interaction; Cell Adhesion; Adaptive Immune System
MBL2	mannose-binding lectin (protein C) 2, soluble	mRNA	Phagocytosis and Degradation; Oxidative Stress; Innate Immune System; Host-pathogen Interaction; Complement System
CYBB	cytochrome b-245, beta polypeptide	mRNA	Phagocytosis and Degradation; Oxidative Stress; NLR signaling; MHC Class I Antigen Presentation; Lymphocyte Trafficking; Innate Immune System; Host-pathogen Interaction; Adaptive Immune System
PTPN22	protein tyrosine phosphatase, non-receptor type 22 (lymphoid)	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Adaptive Immune System
ICOS	inducible T-cell co-stimulator	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Cell Adhesion
CD8A	CD8a molecule	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Cell Adhesion; Adaptive Immune System
CD8B	CD8b molecule	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Cell Adhesion; Adaptive Immune System

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
CTLA4_all	cytotoxic T-lymphocyte-associated protein 4	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Cell Adhesion; Adaptive Immune System
CTLA4-TM	cytotoxic T-lymphocyte-associated protein 4	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Cell Adhesion; Adaptive Immune System
PDCD1	programmed cell death 1	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Cell Adhesion; Adaptive Immune System
sCTLA4	cytotoxic T-lymphocyte-associated protein 4	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Cell Adhesion; Adaptive Immune System
CD247	CD247 molecule	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Host-pathogen Interaction
CD3D	CD3d molecule, delta (CD3-TCR complex)	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Host-pathogen Interaction; Adaptive Immune System
CD3E	CD3e molecule, epsilon (CD3-TCR complex)	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Host-pathogen Interaction; Adaptive Immune System
CD28	CD28 molecule	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Host-pathogen Interaction; Cell Adhesion; Adaptive Immune System
CD45RO	protein tyrosine phosphatase, receptor type, C	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Innate Immune System; Cell Adhesion; Adaptive Immune System
CD45RA	protein tyrosine phosphatase, receptor type, C	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Innate Immune System; Cell Adhesion; Adaptive Immune System
CD45RB	protein tyrosine phosphatase, receptor type, C	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Innate Immune System; Cell Adhesion; Adaptive Immune System
PTPRC_all	protein tyrosine phosphatase, receptor type, C	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Innate Immune System; Cell Adhesion; Adaptive Immune System

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
CD4	CD4 molecule	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Innate Immune System; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
LCP2	lymphocyte cytosolic protein 2 (SH2 domain containing leukocyte protein of 76 kDa)	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Innate Immune System; Hemostasis; Adaptive Immune System
FYN	FYN oncogene related to SRC, FGR, YES	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Hemostasis; Cytokine Signaling; B cell Receptor Signaling; Adaptive Immune System
HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Hemostasis; Cytokine Signaling; Chemokine Signaling; B cell Receptor Signaling; Autophagy; Apoptosis; Adaptive Immune System
RAF1	v-raf-1 murine leukemia viral oncogene homolog 1	mRNA	T Cell Receptor Signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Hemostasis; Cytokine Signaling; Chemokine Signaling; B cell Receptor Signaling; Autophagy; Apoptosis; Adaptive Immune System
ZAP70	zeta-chain (TCR) associated protein kinase 70 kDa	mRNA	T Cell Receptor Signaling; NF- κ B Signaling; Lymphocyte Activation; Adaptive Immune System
CD40LG	CD40 ligand	mRNA	T Cell Receptor Signaling; NF- κ B Signaling; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
BCL10	B-cell CLL/lymphoma 10	mRNA	T Cell Receptor Signaling; NF- κ B Signaling; Lymphocyte Activation; Innate

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
MALT1	mucosa associated lymphoid tissue lymphoma translocation gene 1	mRNA	Immune System; Host-pathogen Interaction; B cell Receptor Signaling; Adaptive Immune System T Cell Receptor Signaling; NF- κ B Signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; B cell Receptor Signaling; Adaptive Immune System
LCK	lymphocyte-specific protein tyrosine kinase	mRNA	T Cell Receptor Signaling; NF- κ B Signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Hemostasis; Cytokine Signaling; Adaptive Immune System
PSMB7	proteasome (prosome, macropain) subunit, beta type, 7	mRNA	T Cell Receptor Signaling; NF- κ B Signaling; MHC Class I Antigen Presentation; Innate Immune System; Immuno-metabolism; Cytokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System
PSMB9	proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional peptidase 2)	mRNA	T Cell Receptor Signaling; NF- κ B Signaling; MHC Class I Antigen Presentation; Innate Immune System; Immuno-metabolism; Cytokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System
PSMC2	proteasome (prosome, macropain) 26S subunit, ATPase, 2	mRNA	T Cell Receptor Signaling; NF- κ B Signaling; MHC Class I Antigen Presentation; Innate Immune System; Immuno-metabolism; Host-pathogen Interaction; Cytokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System
PSMD7	proteasome (prosome, macropain) 26S subunit, non-ATPase, 7	mRNA	T Cell Receptor Signaling; NF- κ B Signaling; MHC Class I Antigen Presentation; Innate Immune System

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
PSMB10	proteasome (prosome, macropain) subunit, beta type, 10	mRNA	System; Immuno-metabolism; Host-pathogen Interaction; Cytokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System T Cell Receptor Signaling; NF- κ B Signaling; MHC Class I Antigen Presentation; Lymphocyte Activation; Innate Immune System; Immuno-metabolism; Cytokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System
PSMB5	proteasome (prosome, macropain) subunit, beta type, 5	mRNA	T Cell Receptor Signaling; Oxidative Stress; NF- κ B Signaling; MHC Class I Antigen Presentation; Innate Immune System; Immuno-metabolism; Cytokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System
SKI	v-ski sarcoma viral oncogene homolog (avian)	mRNA	TGF- β Signaling
SMAD5	SMAD family member 5	mRNA	TGF- β Signaling
IL17A	interleukin 17A	mRNA	Th17 Differentiation; Cytokine Signaling
IL17F	interleukin 17F	mRNA	Th17 Differentiation; Cytokine Signaling
IL1RAP	interleukin 1 receptor accessory protein	mRNA	Th17 Differentiation; Cytokine Signaling
IL22	interleukin 22	mRNA	Th17 Differentiation; Cytokine Signaling
IL6R	interleukin 6 receptor	mRNA	Th17 Differentiation; Cytokine Signaling
IL21	interleukin 21	mRNA	Th17 Differentiation; Lymphocyte Activation; Cytokine Signaling
IL21R	interleukin 21 receptor	mRNA	Th17 Differentiation; Lymphocyte Activation; Cytokine Signaling
IL23R	interleukin 23 receptor	mRNA	Th17 Differentiation; Lymphocyte Activation; Cytokine Signaling
IL6ST	interleukin 6 signal transducer (gp130, oncostatin M receptor)	mRNA	Th17 Differentiation; Lymphocyte Activation; Cytokine Signaling

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
IL23A	interleukin 23, alpha subunit p19	mRNA	Th17 Differentiation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling
IL1R1	interleukin 1 receptor, type I	mRNA	Th17 Differentiation; Oxidative Stress; NF-kB Signaling; Host-pathogen Interaction; Cytokine Signaling
IL12RB1	interleukin 12 receptor, beta 1	mRNA	Th17 Differentiation; Th1 Differentiation; Lymphocyte Activation; Cytokine Signaling
NOTCH1	notch 1	mRNA	Th2 Differentiation; Host-pathogen Interaction
IL4R	interleukin 4 receptor	mRNA	Th2 Differentiation; Lymphocyte Activation; Cytokine Signaling
NOTCH2	notch 2	mRNA	Th2 Differentiation; Lymphocyte Activation; Host-pathogen Interaction
IL13	interleukin 13	mRNA	Th2 Differentiation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling
IL2RA	interleukin 2 receptor, alpha	mRNA	Th2 Differentiation; Lymphocyte Activation; Host-pathogen Interaction; Hemostasis; Cytokine Signaling
IL2RB	interleukin 2 receptor, beta	mRNA	Th2 Differentiation; Lymphocyte Activation; Host-pathogen Interaction; Hemostasis; Cytokine Signaling
IL5	interleukin 5 (colony-stimulating factor, eosinophil)	mRNA	Th2 Differentiation; T Cell Receptor Signaling; Lymphocyte Activation; Hemostasis; Cytokine Signaling
IL4	interleukin 4	mRNA	Th2 Differentiation; T Cell Receptor Signaling; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
IL2	interleukin 2	mRNA	Th2 Differentiation; Th1 Differentiation; T Cell Receptor Signaling; Lymphocyte Activation; Host-pathogen Interaction; Hemostasis; Cytokine Signaling
IL2RG	interleukin 2 receptor, gamma	mRNA	Th2 Differentiation; Th17 Differentiation; Host-pathogen Interaction; Hemostasis; Cytokine Signaling
JAK3	Janus kinase 3	mRNA	Th2 Differentiation; Th17 Differentiation; Lymphocyte Activation; Host-pathogen Interaction; Hemostasis; Cytokine Signaling; Chemokine Signaling
CXCL11	chemokine (C-X-C motif) ligand 11	mRNA	TLR Signaling; Cytokine Signaling; Chemokine Signaling
CXCL9	chemokine (C-X-C motif) ligand 9	mRNA	TLR Signaling; Cytokine Signaling; Chemokine Signaling
SPP1	secreted phosphoprotein 1	mRNA	TLR Signaling; Host-pathogen Interaction
CCL3	chemokine (C-C motif) ligand 3	mRNA	TLR Signaling; Host-pathogen Interaction; Cytokine Signaling; Chemokine Signaling
S100A8	S100 calcium binding protein A8	mRNA	TLR Signaling; Innate Immune System
S100A9	S100 calcium binding protein A9	mRNA	TLR Signaling; Innate Immune System
TLR8	toll-like receptor 8	mRNA	TLR Signaling; Innate Immune System
DUSP4	dual specificity phosphatase 4	mRNA	TLR Signaling; Innate Immune System; Cytokine Signaling
IRAK3	interleukin-1 receptor-associated kinase 3	mRNA	TLR Signaling; Innate Immune System; Cytokine Signaling
SIGIRR	single immunoglobulin and toll-interleukin 1 receptor (TIR) domain	mRNA	TLR Signaling; Innate Immune System; Cytokine Signaling
TOLLIP	toll interacting protein	mRNA	TLR Signaling; Innate Immune System; Cytokine Signaling

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
TLR3	toll-like receptor 3	mRNA	TLR Signaling; Innate Immune System; Host-pathogen Interaction
TLR5	toll-like receptor 5	mRNA	TLR Signaling; Innate Immune System; Host-pathogen Interaction
TLR7	toll-like receptor 7	mRNA	TLR Signaling; Innate Immune System; Host-pathogen Interaction
TLR9	toll-like receptor 9	mRNA	TLR Signaling; Innate Immune System; Host-pathogen Interaction
MAPKAPK2	mitogen-activated protein kinase-activated protein kinase 2	mRNA	TLR Signaling; Innate Immune System; Immuno-metabolism; Cytokine Signaling
CD80	CD80 molecule	mRNA	TLR Signaling; Lymphocyte Activation; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
CD86	CD86 molecule	mRNA	TLR Signaling; Lymphocyte Activation; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
TLR1	toll-like receptor 1	mRNA	TLR Signaling; MHC Class I Antigen Presentation; Innate Immune System; Host-pathogen Interaction; Adaptive Immune System
CCL4	chemokine (C-C motif) ligand 4	mRNA	TLR Signaling; NF- κ B Signaling; Host-pathogen Interaction; Cytokine Signaling; Chemokine Signaling
CD40	CD40 molecule, TNF receptor superfamily member 5	mRNA	TLR Signaling; NF- κ B Signaling; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
LY96	lymphocyte antigen 96	mRNA	TLR Signaling; NF-kB Signaling; MHC Class I Antigen Presentation; Innate Immune System; Host- pathogen Interaction; Apoptosis; Adaptive Immune System
BTK	Bruton agammaglobulinemia tyrosine kinase	mRNA	TLR Signaling; NF-kB Signaling; MHC Class I Antigen Presentation; Lymphocyte Activation; Innate Immune System; B cell Receptor Signaling; Adaptive Immune System
TIRAP	toll-interleukin 1 receptor (TIR) domain containing adaptor protein	mRNA	TLR Signaling; NF-kB Signaling; MHC Class I Antigen Presentation; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Adaptive Immune System
IKBKE	inhibitor of kappa light polypeptide gene enhancer in B- cells, kinase epsilon	mRNA	TLR Signaling; NLR signaling; Innate Immune System; Host- pathogen Interaction
IRAK2	interleukin-1 receptor-associated kinase 2	mRNA	TLR Signaling; NLR signaling; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling
NOD1	nucleotide-binding oligomerization domain containing 1	mRNA	TLR Signaling; NLR signaling; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling
TBK1	TANK-binding kinase 1	mRNA	TLR Signaling; NLR signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling
IL8	interleukin 8	mRNA	TLR Signaling; NLR signaling; NF-kB Signaling; Host- pathogen Interaction; Cytokine Signaling; Chemokine Signaling

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
IRAK1	interleukin-1 receptor-associated kinase 1	mRNA	TLR Signaling; NLR signaling; NF-kB Signaling; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling
IRAK4	interleukin-1 receptor-associated kinase 4	mRNA	TLR Signaling; NLR signaling; NF-kB Signaling; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling
TICAM1	toll-like receptor adaptor molecule 1	mRNA	TLR Signaling; NLR signaling; NF-kB Signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Apoptosis
MYD88	myeloid differentiation primary response gene (88)	mRNA	TLR Signaling; NLR signaling; NF-kB Signaling; MHC Class I Antigen Presentation; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling; Adaptive Immune System
APP	amyloid beta (A4) precursor protein	mRNA	TLR Signaling; Oxidative Stress; NLR signaling; Innate Immune System; Inflammasomes; Hemostasis; Cytokine Signaling
ITGAM	integrin, alpha M (complement component 3 receptor 3 subunit)	mRNA	TLR Signaling; Phagocytosis and Degradation; Lymphocyte Trafficking; Innate Immune System; Host- pathogen Interaction; Hemostasis; Cytokine Signaling; Complement System; Cell Adhesion
ITGB2	integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)	mRNA	TLR Signaling; Phagocytosis and Degradation; Lymphocyte Trafficking; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Hemostasis; Cytokine Signaling; Complement System; Cell Adhesion; Adaptive Immune System

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
TLR2	toll-like receptor 2	mRNA	TLR Signaling; Phagocytosis and Degradation; MHC Class I Antigen Presentation; Innate Immune System; Host-pathogen Interaction; Adaptive Immune System
CTSS	cathepsin S	mRNA	TLR Signaling; Phagocytosis and Degradation; MHC Class II Antigen Presentation; MHC Class I Antigen Presentation; Innate Immune System; Host-pathogen Interaction; Apoptosis; Adaptive Immune System
CD14	CD14 molecule	mRNA	TLR Signaling; Phagocytosis and Degradation; NF- κ B Signaling; MHC Class I Antigen Presentation; Innate Immune System; Host-pathogen Interaction; Apoptosis; Adaptive Immune System
TLR4	toll-like receptor 4	mRNA	TLR Signaling; Phagocytosis and Degradation; NLR signaling; NF- κ B Signaling; MHC Class I Antigen Presentation; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Apoptosis; Adaptive Immune System
CD36	CD36 molecule (thrombospondin receptor)	mRNA	TLR Signaling; Phagocytosis and Degradation; Oxidative Stress; MHC Class I Antigen Presentation; Innate Immune System; Immuno metabolism; Host-pathogen Interaction; Hemostasis; Cytokine Signaling; Adaptive Immune System
TRAF6	TNF receptor-associated factor 6	mRNA	TLR Signaling; T Cell Receptor Signaling; NLR signaling; NF- κ B Signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling; Autophagy;

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
IL12A	interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1, p35)	mRNA	Adaptive Immune System TLR Signaling; Th1 Differentiation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling
IL12B	interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40)	mRNA	TLR Signaling; Th17 Differentiation; Th1 Differentiation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling
CXCL10	chemokine (C-X-C motif) ligand 10	mRNA	TLR Signaling; TNF Family Signaling; Host-pathogen Interaction; Cytokine Signaling; Chemokine Signaling
CASP8	caspase 8, apoptosis-related cysteine peptidase	mRNA	TLR Signaling; TNF Family Signaling; NLR signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Apoptosis
FADD	Fas (TNFRSF6)-associated via death domain	mRNA	TLR Signaling; TNF Family Signaling; NLR signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Apoptosis
NOD2	nucleotide-binding oligomerization domain containing 2	mRNA	TLR Signaling; TNF Family Signaling; NLR signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling
TRAF3	TNF receptor-associated factor 3	mRNA	TLR Signaling; TNF Family Signaling; NLR signaling; NF- κ B Signaling; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling
CCL5	chemokine (C-C motif) ligand 5	mRNA	TLR Signaling; TNF Family Signaling; Oxidative Stress; NLR signaling; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
IKBKB	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta	mRNA	Signaling; Chemokine Signaling TLR Signaling; TNF Family Signaling; T Cell Receptor Signaling; NLR signaling; NF-kB Signaling; MHC Class I Antigen Presentation; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling; Chemokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System
IKBKG	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma	mRNA	TLR Signaling; TNF Family Signaling; T Cell Receptor Signaling; NLR signaling; NF-kB Signaling; MHC Class I Antigen Presentation; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling; Chemokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System
CHUK	conserved helix-loop-helix ubiquitous kinase	mRNA	TLR Signaling; TNF Family Signaling; T Cell Receptor Signaling; Oxidative Stress; NLR signaling; NF-kB Signaling; MHC Class I Antigen Presentation; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling; Chemokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System
MAPK1	mitogen-activated protein kinase 1	mRNA	TLR Signaling; TNF Family Signaling; TGF-b Signaling; T Cell Receptor Signaling; NLR signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Hemostasis;

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
IL1B	interleukin 1, beta	mRNA	Cytokine Signaling; Chemokine Signaling; B cell Receptor Signaling; Autophagy; Apoptosis TLR Signaling; TNF Family Signaling; Th17 Differentiation; Oxidative Stress; NLR signaling; NF-kB Signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling
MAPK11	mitogen-activated protein kinase 11	mRNA	TLR Signaling; TNF Family Signaling; Th17 Differentiation; T Cell Receptor Signaling; NLR signaling; Lymphocyte Trafficking; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling
MAPK14	mitogen-activated protein kinase 14	mRNA	TLR Signaling; TNF Family Signaling; Th17 Differentiation; T Cell Receptor Signaling; NLR signaling; Lymphocyte Trafficking; Innate Immune System; Host- pathogen Interaction; Hemostasis; Cytokine Signaling
TNF	tumor necrosis factor	mRNA	TLR Signaling; TNF Family Signaling; Th17 Differentiation; TGF- Signaling; T Cell Receptor Signaling; Oxidative Stress; NLR signaling; NF-kB Signaling; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling; Apoptosis
IL6	interleukin 6 (interferon, beta 2)	mRNA	TLR Signaling; TNF Family Signaling; Th2 Differentiation; Th17 Differentiation; Oxidative Stress; NLR signaling; Lymphocyte Activation; Host- pathogen

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
			Interaction; Cytokine Signaling
MAP4K1	mitogen-activated protein kinase kinase kinase kinase 1	mRNA	TNF Family Signaling
MAP4K2	mitogen-activated protein kinase kinase kinase kinase 2	mRNA	TNF Family Signaling
MAP4K4	mitogen-activated protein kinase kinase kinase kinase 4	mRNA	TNF Family Signaling
CSF1	colony stimulating factor 1 (macrophage)	mRNA	TNF Family Signaling; Cytokine Signaling
LIF	leukemia inhibitory factor (cholinergic differentiation factor)	mRNA	TNF Family Signaling; Cytokine Signaling
CCL20	chemokine (C-C motif) ligand 20	mRNA	TNF Family Signaling; Cytokine Signaling; Chemokine Signaling
CX3CL1	chemokine (C-X3-C motif) ligand 1	mRNA	TNF Family Signaling; Cytokine Signaling; Chemokine Signaling
SELE	selectin E	mRNA	TNF Family Signaling; Host-pathogen Interaction; Hemostasis; Cell Adhesion
TNFRSF1B	tumor necrosis factor receptor superfamily, member 1B	mRNA	TNF Family Signaling; Innate Immune System; Cytokine Signaling
CASP10	caspase 10, apoptosis-related cysteine peptidase	mRNA	TNF Family Signaling; Innate Immune System; Host-pathogen Interaction; Apoptosis
IL18R1	interleukin 18 receptor 1	mRNA	TNF Family Signaling; Lymphocyte Activation; Cytokine Signaling
IL15	interleukin 15	mRNA	TNF Family Signaling; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling
TNFSF10	tumor necrosis factor (ligand) superfamily, member 10	mRNA	TNF Family Signaling; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Apoptosis
TRAF4	TNF receptor-associated factor 4	mRNA	TNF Family Signaling; NF- κ B Signaling
TRAF1	TNF receptor-associated factor 1	mRNA	TNF Family Signaling; NF- κ B Signaling; Host-pathogen Interaction; Apoptosis
LTA	lymphotoxin alpha (TNF superfamily, member 1)	mRNA	TNF Family Signaling; NF- κ B Signaling; Host-pathogen Interaction; Cytokine Signaling
CXCL1	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	mRNA	TNF Family Signaling; NLR signaling; Innate Immune System; Host-pathogen Interaction; Cytokine

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
CCL2	chemokine (C-C motif) ligand 2	mRNA	Signaling; Chemokine Signaling TNF Family Signaling; NLR signaling; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling; Chemokine Signaling
TRAF5	TNF receptor-associated factor 5	mRNA	TNF Family Signaling; NLR signaling; NF-kB Signaling; Host- pathogen Interaction
CXCL2	chemokine (C-X-C motif) ligand 2	mRNA	TNF Family Signaling; NLR signaling; NF-kB Signaling; Host- pathogen Interaction; Cytokine Signaling; Chemokine Signaling
CASP3	caspase 3, apoptosis-related cysteine peptidase	mRNA	TNF Family Signaling; Oxidative Stress; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling; Apoptosis
FAS	Fas (TNF receptor superfamily, member 6)	mRNA	TNF Family Signaling; Oxidative Stress; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling; Apoptosis
PTGS2	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	mRNA	TNF Family Signaling; Oxidative Stress; NF-kB Signaling; Immuno- metabolism; Host- pathogen Interaction; Cytokine Signaling
TNFAIP3	tumor necrosis factor, alpha- induced protein 3	mRNA	TNF Family Signaling; Oxidative Stress; NLR signaling; NF-kB Signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction
TRAF2	TNF receptor-associated factor 2	mRNA	TNF Family Signaling; Oxidative Stress; NLR signaling; NF-kB Signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling; Apoptosis
CSF2	colony stimulating factor 2 (granulocyte-macrophage)	mRNA	TNF Family Signaling; T Cell Receptor Signaling; Lymphocyte Activation; Host- pathogen Interaction; Hemostasis; Cytokine Signaling

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
BATF3	basic leucine zipper transcription factor, ATF-like 3	mRNA	Transcriptional Regulation
GFI1	growth factor independent 1 transcription repressor	mRNA	Transcriptional Regulation
IKZF2	IKAROS family zinc finger 2 (Helios)	mRNA	Transcriptional Regulation
ILF3	interleukin enhancer binding factor 3, 90 kDa	mRNA	Transcriptional Regulation
NFIL3	nuclear factor, interleukin 3 regulated	mRNA	Transcriptional Regulation
NFKBIZ	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta	mRNA	Transcriptional Regulation
PAX5	paired box 5	mRNA	Transcriptional Regulation
RUNX1	runt-related transcription factor 1	mRNA	Transcriptional Regulation
TAL1	T-cell acute lymphocytic leukemia 1	mRNA	Transcriptional Regulation
TCF4	transcription factor 4	mRNA	Transcriptional Regulation
EGR2	early growth response 2	mRNA	Transcriptional Regulation; Host-pathogen Interaction
PPARG	peroxisome proliferator-activated receptor gamma	mRNA	Transcriptional Regulation; Immuno-metabolism
EOMES	eomesodermin	mRNA	Transcriptional Regulation; Lymphocyte Activation
IKZF1	IKAROS family zinc finger 1 (Ikaros)	mRNA	Transcriptional Regulation; Lymphocyte Activation
IKZF3	IKAROS family zinc finger 3 (Aiolos)	mRNA	Transcriptional Regulation; Lymphocyte Activation
LEF1	lymphoid enhancer-binding factor 1	mRNA	Transcriptional Regulation; Lymphocyte Activation
POU2F2	POU class 2 homeobox 2	mRNA	Transcriptional Regulation; Lymphocyte Activation
BATF	basic leucine zipper transcription factor, ATF-like	mRNA	Transcriptional Regulation; Lymphocyte Activation; Cytokine Signaling
ZEB1	zinc finger E-box binding homeobox 1	mRNA	Transcriptional Regulation; Lymphocyte Activation; Cytokine Signaling
TCF7	transcription factor 7 (T-cell specific, HMG-box)	mRNA	Transcriptional Regulation; Lymphocyte Activation; Host-pathogen Interaction
RELB	v-rel reticuloendotheliosis viral oncogene homolog B	mRNA	Transcriptional Regulation; NF-kB Signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling
ETS1	v-ets erythroblastosis virus E26 oncogene homolog 1 (avian)	mRNA	Transcriptional Regulation; Oxidative Stress; Host-pathogen Interaction

101**102**

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
TP53	tumor protein p53	mRNA	Transcriptional Regulation; Oxidative Stress; Host-pathogen Interaction; Hemostasis; Cytokine Signaling; Apoptosis
XBP1	X-box binding protein 1	mRNA	Transcriptional Regulation; Oxidative Stress; Lymphocyte Activation; Host-pathogen Interaction
NFATC3	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 3	mRNA	Transcriptional Regulation; T Cell Receptor Signaling; Innate Immune System; Host-pathogen Interaction; B cell Receptor Signaling; Adaptive Immune System
NFATC1	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1	mRNA	Transcriptional Regulation; T Cell Receptor Signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; B cell Receptor Signaling; Adaptive Immune System
NFATC2	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2	mRNA	Transcriptional Regulation; T Cell Receptor Signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; B cell Receptor Signaling; Adaptive Immune System
STAT4	signal transducer and activator of transcription 4	mRNA	Transcriptional Regulation; Th1 Differentiation; Host-pathogen Interaction; Cytokine Signaling
TBX21	T-box 21	mRNA	Transcriptional Regulation; Th1 Differentiation; Lymphocyte Activation
RORC	RAR-related orphan receptor C	mRNA	Transcriptional Regulation; Th17 Differentiation; Lymphocyte Activation; Cytokine Signaling
AHR	aryl hydrocarbon receptor	mRNA	Transcriptional Regulation; Th17 Differentiation; Lymphocyte Activation; Immuno-metabolism

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
MAF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian)	mRNA	Transcriptional Regulation; Th2 Differentiation
STAT5A	signal transducer and activator of transcription 5A	mRNA	Transcriptional Regulation; Th2 Differentiation; Host-pathogen Interaction; Cytokine Signaling
GATA3	GATA binding protein 3	mRNA	Transcriptional Regulation; Th2 Differentiation; Lymphocyte Activation; Hemostasis; Cytokine Signaling
STAT5B	signal transducer and activator of transcription 5B	mRNA	Transcriptional Regulation; Th2 Differentiation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Chemokine Signaling
STAT6	signal transducer and activator of transcription 6, interleukin-4 induced	mRNA	Transcriptional Regulation; Th2 Differentiation; Oxidative Stress; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling
NFKB2	nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)	mRNA	Transcriptional Regulation; TLR Signaling; NLR signaling; NF- κ B Signaling; Innate Immune System; Inflammasomes; Host-pathogen Interaction; Cytokine Signaling
NFKBIA	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	mRNA	Transcriptional Regulation; TLR Signaling; TNF Family Signaling; T Cell Receptor Signaling; NLR signaling; NF- κ B Signaling; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling; Chemokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System
NFKB1	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	mRNA	Transcriptional Regulation; TLR Signaling; TNF Family Signaling; Th1 Differentiation; T Cell Receptor Signaling; Oxidative Stress; NLR signaling; NF- κ B Signaling; Innate Immune

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
RELA	v-rel reticuloendotheliosis viral oncogene homolog A (avian)	mRNA	System; Inflammasomes; Host-pathogen Interaction; Cytokine Signaling; Chemokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System Transcriptional Regulation; TLR Signaling; TNF Family Signaling; Th 1 Differentiation; T Cell Receptor Signaling; Oxidative Stress; NLR signaling; NF-kB Signaling; Innate Immune System; Inflammasomes; Host-pathogen Interaction; Cytokine Signaling; Chemokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System Transcriptional Regulation; TNF Family Signaling; Lymphocyte Activation
BCL3	B-cell CLL/lymphoma 3	mRNA	Transcriptional Regulation; TNF Family Signaling; Lymphocyte Activation
CEPB	CCAAT/enhancer binding protein (C/EBP), beta	mRNA	Transcriptional Regulation; TNF Family Signaling; Lymphocyte Activation; Host-pathogen Interaction
IL10RA	interleukin 10 receptor, alpha	mRNA	Treg Differentiation; Host-pathogen Interaction; Cytokine Signaling
IL10	interleukin 10	mRNA	Treg Differentiation; T Cell Receptor Signaling; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling
TGFBR1	transforming growth factor, beta receptor 1	mRNA	Treg Differentiation; Th17 Differentiation; TGF-b Signaling; Host- pathogen Interaction; Cytokine Signaling
SMAD3	SMAD family member 3	mRNA	Treg Differentiation; Th17 Differentiation; TGF-b Signaling; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling
TGFBR2	transforming growth factor, beta receptor II (70/80 kDa)	mRNA	Treg Differentiation; Th17 Differentiation; TGF-b Signaling; Lymphocyte Activation; Host- pathogen

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
TGFB1	transforming growth factor, beta 1	mRNA	Interaction; Cytokine Signaling Treg Differentiation; Th17 Differentiation; TGF- β Signaling; Lymphocyte Activation; Host-pathogen Interaction; Hemostasis; Cytokine Signaling
FOXP3	forkhead box P3	mRNA	Treg Differentiation; Transcriptional Regulation; Lymphocyte Activation
STAT3	signal transducer and activator of transcription 3 (acute-phase response factor)	mRNA	Treg Differentiation; Transcriptional Regulation; Th17 Differentiation; Host-pathogen Interaction; Cytokine Signaling; Chemokine Signaling
IFI35	interferon-induced protein 35	mRNA	Type I Interferon Signaling; Cytokine Signaling
IFIT2	interferon-induced protein with tetratricopeptide repeats 2	mRNA	Type I Interferon Signaling; Cytokine Signaling
IFITM1mcfarlin@unt.edu	interferon induced transmembrane protein 1 (9-27)	mRNA	Type I Interferon Signaling; Cytokine Signaling; B cell Receptor Signaling; Adaptive Immune System
MX1	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)	mRNA	Type I Interferon Signaling; Host-pathogen Interaction; Cytokine Signaling
BST2	bone marrow stromal cell antigen 2	mRNA	Type I Interferon Signaling; Lymphocyte Activation; Innate Immune System; Cytokine Signaling
PSMB8	proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional peptidase 7)	mRNA	Type I Interferon Signaling; T Cell Receptor Signaling; NF- κ B Signaling; MHC Class I Antigen Presentation; Innate Immune System; Immunometabolism; Cytokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System
IFNA1/13	interferon, alpha 1/interferon, alpha 13	mRNA	Type I Interferon Signaling; TLR Signaling; NLR signaling; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling
IFNAR1	interferon (alpha, beta and omega) receptor 1	mRNA	Type I Interferon Signaling; TLR Signaling; NLR signaling; Lymphocyte Activation; Host-

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
IFNAR2	interferon (alpha, beta and omega) receptor 2	mRNA	pathogen Interaction; Cytokine Signaling Type I Interferon Signaling; TLR Signaling; NLR signaling; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling
IFNA2	interferon, alpha 2	mRNA	Type I Interferon Signaling; TLR Signaling; NLR signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Hemostasis; Cytokine Signaling
IFNB1	interferon, beta 1, fibroblast	mRNA	Type I Interferon Signaling; TLR Signaling; NLR signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Hemostasis; Cytokine Signaling
EGR1	early growth response 1	mRNA	Type I Interferon Signaling; Transcriptional Regulation; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling
STAT2	signal transducer and activator of transcription 2, 113 kDa	mRNA	Type I Interferon Signaling; Transcri ptional Regulation; NLR signaling; Host- pathogen Interaction; Cytokine Signaling; Chemokine Signaling
TYK2	tyrosine kinase 2	mRNA	Type I Interferon Signaling; Treg Differentiation; Th17 Differentiation; Th1 Differentiation; NLR signaling; Host- pathogen Interaction; Cytokine Signaling
NCAM1	neural cell adhesion molecule 1	mRNA	Type II Interferon Signaling; Cytokine Signaling; Cell Adhesion
CIITA	class II, major histocompatibility complex, transactivator	mRNA	Type II Interferon Signaling; Host- pathogen Interaction; Cytokine Signaling
PTAFR	platelet-activating factor receptor	mRNA	Type II Interferon Signaling; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
CD44	CD44 molecule (Indian blood group)	mRNA	Type II Interferon Signaling; Innate Immune System; Immuno-metabolism; Host-pathogen Interaction; Hemostasis; Cytokine Signaling
B2M	beta-2-microglobulin	mRNA	Type II Interferon Signaling; MHC Class I Antigen Presentation; Lymphocyte Activation; Innate Immune System; Cytokine Signaling; Adaptive Immune System
GBP1	guanylate binding protein 1, interferon-inducible	mRNA	Type II Interferon Signaling; NLR signaling; Cytokine Signaling
GBP5	guanylate binding protein 5	mRNA	Type II Interferon Signaling; NLR signaling; Cytokine Signaling
PML	promyelocytic leukemia	mRNA	Type II Interferon Signaling; Oxidative Stress; Host-pathogen Interaction; Cytokine Signaling
PRKCD	protein kinase C, delta	mRNA	Type II Interferon Signaling; Oxidative Stress; NLR signaling; Lymphocyte Activation; Innate Immune System; Hemostasis; Cytokine Signaling; Chemokine Signaling; Autophagy; Apoptosis
FCGR1A/B	Fc fragment of IgG, high affinity Ia, receptor (CD64)/Fc fragment of IgG, high affinity Ib, receptor (CD64)	mRNA	Type II Interferon Signaling; Phagocytosis and Degradation; MHC Class I Antigen Presentation; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling; Adaptive Immune System
HLA-DPA1	major histocompatibility complex, class II, DP alpha 1	mRNA	Type II Interferon Signaling; T Cell Receptor Signaling; Phagocytosis and Degradation; MHC Class II Antigen Presentation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
HLA-DPB1	major histocompatibility complex, class II, DP beta 1	mRNA	Type II Interferon Signaling; T Cell Receptor Signaling; Phagocytosis and Degradation; MHC Class II Antigen

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	mRNA	Presentation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System Type II Interferon Signaling; T Cell Receptor Signaling; Phagocytosis and Degradation; MHC Class II Antigen Presentation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	mRNA	Type II Interferon Signaling; T Cell Receptor Signaling; Phagocytosis and Degradation; MHC Class II Antigen Presentation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
HLA-DRA	major histocompatibility complex, class II, DR alpha	mRNA	Type II Interferon Signaling; T Cell Receptor Signaling; Phagocytosis and Degradation; MHC Class II Antigen Presentation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
HLA-DRB1	major histocompatibility complex, class II, DR beta 1	mRNA	Type II Interferon Signaling; T Cell Receptor Signaling; Phagocytosis and Degradation; MHC Class II Antigen Presentation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
HLA-DRB3	major histocompatibility complex, class II, DR beta 3	mRNA	Type II Interferon Signaling; T Cell Receptor Signaling; Phagocytosis and Degradation; MHC Class II Antigen

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
IFNGR1	interferon gamma receptor 1	mRNA	Presentation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System Type II Interferon Signaling; Th1 Differentiation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling
IFNG	interferon, gamma	mRNA	Type II Interferon Signaling; Th1 Differentiation; TGF- β Signaling; T Cell Receptor Signaling; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling
JAK2	Janus kinase 2	mRNA	Type II Interferon Signaling; Th17 Differentiation; Th1 Differentiation; Oxidative Stress; Host-pathogen Interaction; Hemostasis; Cytokine Signaling; Chemokine Signaling
ICAM1	intercellular adhesion molecule 1	mRNA	Type II Interferon Signaling; TNF Family Signaling; NF- κ B Signaling; Lymphocyte Trafficking; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
VCAM1	vascular cell adhesion molecule 1	mRNA	Type II Interferon Signaling; TNF Family Signaling; NF- κ B Signaling; Lymphocyte Trafficking; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
HLA-A	major histocompatibility complex, class I, A	mRNA	Type II Interferon Signaling; Type I Interferon Signaling; Phagocytosis and Degradation; MHC Class I Antigen Presentation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
HLA-B	major histocompatibility complex, class I, B	mRNA	Type II Interferon Signaling; Type I Interferon Signaling; Phagocytosis and

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
HLA-C	major histocompatibility complex, class I, C	mRNA	Degradation; MHC Class I Antigen Presentation; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System Type II Interferon Signalning; Type I Interferon Signalning; Phagocytosis and Degradation; MHC Class I Antigen Presentation; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System
PTPN6	protein tyrosine phosphatase, non-receptor type 6	mRNA	Type II Interferon Signalning; Type I Interferon Signalning; T Cell Receptor Signalning; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Hemostasis; Cytokine Signalning; B cell Receptor Signalning; Adaptive Immune System
SOCS1	suppressor of cytokine signaling 1	mRNA	Type II Interferon Signalning; Type I Interferon Signalning; TLR Signalning; MHC Class I Antigen Presentation; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling; Adaptive Immune System
SOCS3	suppressor of cytokine signaling 3	mRNA	Type II Interferon Signalning; Type I Interferon Signalning; TNF Family Signalning; MHC Class I Antigen Presentation; Host-pathogen Interaction; Cytokine Signaling; Adaptive Immune System
IRF8	interferon regulatory factor 8	mRNA	Type II Interferon Signalning; Type I Interferon Signalning; Transcriptional Regulation; Host-pathogen Interaction; Cytokine Signaling

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
IRF1	interferon regulatory factor 1	mRNA	Type II Interferon Signaling; Type I Interferon Signaling; Transcriptional Regulation; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Hemostasis; Cytokine Signaling
IRF4	interferon regulatory factor 4	mRNA	Type II Interferon Signaling; Type I Interferon Signaling; Transcriptional Regulation; Th17 Differentiation; Lymphocyte Activation; Cytokine Signaling
IRF5	interferon regulatory factor 5	mRNA	Type II Interferon Signaling; Type I Interferon Signaling; Transcriptional Regulation; TLR Signaling; Cytokine Signaling
IRF3	interferon regulatory factor 3	mRNA	Type II Interferon Signaling; Type I Interferon Signaling; Transcriptional Regulation; TLR Signaling; NLR signaling; Innate Immune System; Host- pathogen Interaction; Hemostasis; Cytokine Signaling
IRF7	interferon regulatory factor 7	mRNA	Type II Interferon Signaling; Type I Interferon Signaling; Transcriptional Regulation; TLR Signaling; NLR signaling; Innate Immune System; Host- pathogen Interaction; Hemostasis; Cytokine Signaling
STAT1	signal transducer and activator of transcription 1, 91 kDa	mRNA	Type II Interferon Signaling; Type I Interferon Signaling; Transcriptional Regulation; TLR Signaling; Th1 Differentiation; NLR signaling; Host- pathogen Interaction; Cytokine Signaling; Chemokine Signaling
JAK1	Janus kinase 1	mRNA	Type II Interferon Signaling; Type I Interferon Signaling; Treg Differentiation; Th17 Differentiation; Th1

121

SUPPLEMENTARY TABLE 3-continued

Summary of Nanostring Array RNA Biomarkers			
Abbreviation	Name	Type	Relevance
		Differentiation; NLR signaling; Host-pathogen Interaction; Hemostasis; Cytokine Signaling	

The invention claimed is:

1. A composition comprising a combination of a curcumin extract and a pomegranate extract, wherein said combination is a ratio of curcumin extract:pomegranate extract of 1:1 (w/w),
 the curcumin extract containing 20-25% by weight *Curcuma longa* extract, 19-35% by weight maltodextrin, 10-20% by weight lecithin, 1-35% by weight stearic acid or salts thereof, 1-3% by weight ascorbyl palmitate, and optionally, 0.3-3% by weight silicon dioxide, the curcumin extract comprises solid lipid curcumin particles, the curcumin extract having a standardization of not less than about 20% total curcuminoids, and the pomegranate extract containing 100% by weight *Punica granatum* fruit extract, the pomegranate extract having a standardization of not less than about 10% punicalagins and 40% total polyphenols;
 wherein radical scavenging activity measured by DPPH assay in micromole Trolox equivalents per gram (micromole TE/gram) is about 15% greater compared to a combination having a ratio of curcumin extract:pomegranate extract of 1:1.5 (w/w), and wherein levels of both inflammatory biomarkers IL-4 and IL-8 are increased relative to control when administered to a human subject.
2. The composition of claim 1, said combination comprising 20-30% by weight curcuminoids and 10-50% by weight punicalagins.
3. The composition of claim 2, said combination comprising not less than 20% w/w total curcuminoids, not less than 10% w/w punicalagins, and 40-50% w/w total pomegranate polyphenols.
4. A method of supporting and/or improving immune health in a subject, comprising the steps of
 - a. providing a composition of claim 1, and
 - b. administering an effective amount of the composition to a subject in need thereof to support and/or improve the immune system of the subject.
5. The method of claim 4, wherein said subject is a healthy subject and exercises regularly.

122

6. The method of claim 4, wherein said subject is a healthy subject and is sedentary.
7. The method of claim 4, where the subject is not a healthy subject.
8. The method of claim 4, wherein in step b, infection risk is reduced in the subject.
9. The method of claim 4, wherein in step b, gut health is improved in the subject.
10. A method of treating an immune-related disease or disorder in a subject, and a symptom thereof, comprising the steps of
 - a. providing a composition of claim 1, and
 - b. administering an effective amount of the composition to the subject.
11. The method of claim 10, wherein said disease or disorder is caused by a viral infection.
12. The method of claim 11, wherein said disease or disorder is COVID 19.
13. The method of claim 10, wherein said disease or disorder is sepsis.
14. A method of immunomodulating the immune system of a subject, comprising the steps of
 - a. providing a composition of claim 1, and
 - b. administering an effective amount of the composition to the subject.
15. The composition of claim 1, said composition including 20-32% total pomegranate polyphenols, 3-5% bis and dimethoxy curcumin, 12-13% curcumin, 9-30% punicalagins, 10-16% stearic and palmitic acid, 1-2% ascorbyl palmitate, 10-16% dextrin, 15-20% polysaccharides, and 1-3% phosphatidylcholine.
16. The composition of claim 1, wherein said composition is a dietary supplement.
17. The composition of claim 1, wherein said composition is a powder.
18. The composition of claim 1, said composition comprising 500 mg of said combination.
19. The composition of claim 1, said composition comprising 1000 mg of said combination.

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