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Polyphenol blend of curcumin extract and pomegranate extract and methods of improving immune response

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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References Cited

U.S. PATENT DOCUMENTS

Patent No.	Issued Date	Patentee Name	U.S. Cl.	CPC
7638640	12/2008	Seeram et al.	N/A	N/A
7897791	12/2010	Seeram et al.	N/A	N/A
7919636	12/2010	Seeram et al.	N/A	N/A
8535738	12/2012	Collins	424/735	A61K 36/575
9192644	12/2014	Frautschy et al.	N/A	N/A
10588866	12/2019	Tingorani et al.	N/A	N/A
2004/0156920	12/2003	Kane	424/754	A01N 63/10
2008/0268095	12/2007	Herzog	426/2	A61P 3/02
2009/0110789	12/2008	Mower	426/330.5	A23L 33/105

FOREIGN PATENT DOCUMENTS

Patent No.	Application Date	Country	CPC
1993365	12/2012	EP	N/A
1993365	12/2012	EP	N/A

OTHER PUBLICATIONS

ProHealth (https://www.amazon.com/ProHealth-Optimized-Curcumin-Longvida-Pomegranate/dp/B06XHSTRWP) (Year: 2017). cited by examiner

Eidenberger, T. 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) (4 pages). cited by applicant

Nahar et al., “Anti-Inflammatory Effects of Novel Standardized Solid Lipid Curcumin Formulations” J. Med. Food, 18(7): 786-792 (2015). cited by applicant

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., 72(4): 499-510 (2021). cited by applicant

Machida et al., “Effects of solid, lipid curcumin particles on alcohol metabolism—an exploratory and a randomized, double-blind, placebo-controlled, parallel-group crossover study” Pharmacology and Treatment (JPT), 48(5): 867-73 (2020) [Abstract Only]. cited by applicant

Eidenberger, “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) (2 pages). cited by applicant

McFarlin et al., “Reduced inflammatory and muscle damage biomarkers following oral supplementation with bioavailable curcumin” BBA Clin., 18(5):72-8 (2016). cited by applicant

Nicol et al., “Curcumin supplementation likely attenuates delayed onset muscle soreness (DOMS)” Eur J Appl Physiol., 115(8): 1769-77 (2015). cited by applicant

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). cited by applicant
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). cited by applicant
McFarlin et al., “Does acute improvement in muscle recovery with curcumin supplementation translate to Long-term Training?” Journal of Science in Sport and Exercise, 1:203-207 (2019), pp. 1-5. cited by applicant
Sciberras 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) (10 pages). cited by applicant
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). cited by applicant
Drobnic et al., “Reduction of delayed onset muscle soreness by a novel curcumin delivery system (Meriva(R)): a randomized, placebo-controlled trial” J. Int. Soc. Sports. Nutr., 11:31 (2014) (10 pages). cited by applicant
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). cited by applicant
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). cited by applicant
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):171-83 (2013). cited by applicant
Bergendiova et al., “Pleuran (beta-glucan from Pleurotus osreatus) supplementation, cellular immune response and respiratory tract infections in athletes” Eur. J. Appl. Physiol., 111(9): 2033-40 (2011). cited by applicant
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):410-17 (2012). cited by applicant
Bell et al., “Recovery facilitation with Montmorency cherries following high-intensity, metabolically challenging exercise” Appl. Physiol. Nutr. Metab., 40(4): 414-23 (2015). cited by applicant
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) (12 pages). cited by applicant
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). cited by applicant
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). cited by applicant
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):451-57 (2013). cited by applicant
Gleeson, “Immune function in sport and exercise” J. Appl. Physiol., 103: 693-99 (2007). cited by applicant
Walsh et al., “Position statement part one: Immune function and exercise” Exercise Immunology Review, 17: 6-63 (2011). cited by applicant
Walsh et al., “Position statement part two: Maintaining immune health” Exercise Immunology

Review, 17: 64-103 (2011). cited by applicant
Gleeson et al., “Sex differences in immune variables and respiratory infection incidence in an athletic population” Exercise Immunology Review, 17: 122-135 (2011). cited by applicant
Ogawa et al., “Plasma adenosine triphosphate and heat shock protein 72 concentrations after aerobic and eccentric exercise” Exercise Immunology Review, 17: 136-149 (2011). cited by applicant
Maltseva et al., “Killer cell immunoglobulin-like receptors and exercise” Exercise Immunology Review, 17: 150-163 (2011). cited by applicant
Gillum et al., “A review of sex differences in immune function after aerobic exercise” Exercise Immunol. Rev. 17: 104-121 (2011). cited by applicant
Genetic Engineering & Biotechnology News, “Gut Microbiome—Pomegranate Partnership Reduces Colitis”, https://www.genengnews.com/news/gut-microbiome-pomegranate-partnership-reduces-colitis-in-mice/ (Jan. 10, 2019) (5 pages) [Version available online as of Jun. 17, 2022]. cited by applicant
Li et al., “Pomegranate ellagitannins stimulate growth of gut bacteria in vitro: Implications for prebiotic and metabolic effects”, Anaerobe, Aug. 2015;34:164-168 [Abstract Only]. cited by applicant
Paddock, “Gut bacteria unleash anti-aging power of pomegranates”, Medical News Today https://www.medicalnewstoday.com/articles/311572# Urolithin-A-is-the-only-molecule-that-can-relaunch-mitophagy, (3 pages) [Version available online as of Jun. 17, 2022]. cited by applicant

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Background/Summary

CROSS-REFERENCE TO RELATED APPLICATIONS (1) 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
(1) 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
(2) 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).
(3) 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-κb). 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).

(4) 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-κb, and tumor necrosis factor alpha (TNFα). Pomegranate fruit 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)].

(5) 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

(6) 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®.

(7) 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.

(8) 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.

(9) 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.

(10) 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.

(11) 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.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

(1) 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).

(2) 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).

(3) 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).

(4) 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).

(5) 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).
(6) 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).
(7) 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), Restoridyn® (shaded), overlap (striped).
(8) 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).
(9) 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).
(10) 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).
(11) 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
(12) 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 curcuminoids, 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.
(13) 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.
(14) 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 among 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-κB 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.

(15) 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.

(16) 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.

(17) 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 252.sup.nd 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.

(18) 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.

(19) Solid Lipid Nanoparticles (SLN) Preparation

(20) Starting Formula.

(21) 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.

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

(23) 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.

(24) 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.

(25) In an embodiment, an enzyme capable of hydrolyzing punicalagins and/or punicalins 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.

(26) 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. 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®.

(27) 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 punicalins 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.

(28) 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.

(29) 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.

(30) 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.

(31) 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.

(32) 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.

(33) 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:

(34) TABLE-US-00001 TABLE 1 Composition Curcumin Extract Pomegranate Extract 25-35% *Curcuma longa* extract 100% *Punica granatum* extract of fruit 10-20% lecithin 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.
(35) 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:
(36) TABLE-US-00002 TABLE 2 Composition Curcumin Extract Pomegranate Extract 20-35% *Curcuma longa* extract 100% *Punica granatum* extract of fruit 19-35% maltodextrin 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.
(37) 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.
(38) 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 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.
(39) 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®.
(40) 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.

(41) 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.

(42) 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 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.

(43) 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.

(44) 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.

(45) 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.

(46) “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 pomegranate 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.

(47) 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.

(48) “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.

(49) 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.

(50) Treating or preventing an immune disease or disorder according 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.

(51) 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.

(52) 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 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.

(53) 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.

Example 1

Materials & Methods

(54) Experimental Design

(55) 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 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.

(56) 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 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)).

(57) 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 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 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)].

(58) Subjects

(59) 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.

(60) TABLE-US-00003 TABLE 3 Subject Characteristics Control Treatment Gender Male = 5, Female = 5 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:

(61) Whole blood was collected from a peripheral arm vein into Z-serum separator vacuettes (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.

(62) Experiment One: Bead-Based Analysis

(63) 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).

(64) Experiment One: Statistical Analysis

(65) 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.

(66) Experiment Two: Nanostring Analysis

(67) 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.

(68) Experiment Two: Statistical Analysis

(69) 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

(70) Experiment One: Protein Analysis

(71) 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.

(72) Experiment One: Bead-Based RNA Analysis

(73) 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.

(74) Experiment Two: Nanostring mRNA Analysis

(75) 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

(76) 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.

(77) 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; $p \leq 0.001$). 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).

(78) 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; $p \leq 0.01$), 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; $p \leq 0.05$). 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.

(79) 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.

(80) 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-b 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**.

(81) 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).].
(82) 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); Drobnic 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 HSP*70 *after an Ironman Triathlon race" Eur. J. Appl. Physiol.* 98(6):525-34 (2006)].
(83) 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, CXC3CL1, 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 TNFα (TNFSF14, TRAF6, and THRIL), nuclear factor kappa beta (NF-κβ) 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).
(84) 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.

(85) 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)].

(86) 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.

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

(88) 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≤0.05); **(p≤0.01); ***(p≤0.001); ****(p≤0.0001).

(89) 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.).

(90) 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≤0.05); **(p≤0.01); ***(p≤0.001); ****(p≤0.0001).

(91) 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®).

(92) 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≤0.05); **(p≤0.01); ***(p≤0.001); **** (p≤0.0001).

Example 2

(93) 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.

(94) 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).

(95) 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 $p<0.05$.

(96) 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.

(97) TABLE-US-00004 TABLE 4 PRE-Half-Marathon TABLE - PRE Significant mRNA Upregulated/ targets ($p < 0.05$) Official Name Downregulated CD3EAP CD3e molecule, epsilon Down associated protein C4A/B complement Up component 4A/complement component 4B CX3CR1 chemokine (C-X3-C Down motif) receptor 1 TIRAP toll-interleukin 1 Up receptor, domain containing adaptor protein TNFSF4 tumor necrosis factor Up (ligand) superfamily, member 4 IRAK3 interleukin-1 receptor- Up associated kinase 3 RAG1 recombination Up activating gene 1 IL2RG interleukin 2 receptor, Down gamma TNFSF15 tumor necrosis factor Up (ligand) superfamily, member 15 CD55 CD55 molecule, decay Up accelerating factor for complement ARG2 arginase, type II Up C5 complement Up component 5 TNFSF8 tumor necrosis factor Up (ligand) superfamily, member 8 PTK2 PTK2 protein tyrosine Up Kinase 2 FKBP5 FK506 binding protein Up 5 C6 compliment Up component 6 TNFRSF17 tumor necrosis factor Up receptor superfamily, member 17 ITGAE integrin, alpha E Up ARG1 arginase, liver Up C1S complement Up component 1, s subcomponent GP1BB glycoprotein 1b Up (platelet), beta polypeptide GATA3 GATA binding protein 3 Up CD24 CD24 molecule Up FOXP3 forkhead box P3 Up

(98) TABLE-US-00005 TABLE 5 4 Hours after Half-Marathon Significant mRNA Upregulated/ targets ($p < 0.05$) Official Name Downregulated IL28A interleukin 28A Down (interferon, lambda 2) CSF1 colony stimulating Down factor 1 (macrophage) BAX BCL2-associated X Down protein IFITM1 interferon induced Up transmembrane protein 1 GPR183 G protein-coupled Up receptor 183 CXCL12 chemokine (C-X-C Up motif) ligand 12 CASP3 caspase 3, apoptosis- Up related cysteine peptidase CASP2 caspase 2, apoptosis- Down related cysteine peptidase PDCD1 programmed cell death Down 1 LY96 lymphocyte antigen 96 Up CD3D CD3d molecule, delta Up (CD3-TCR complex) B2M Beta-2-microglobulin Up C9 complement Down component 9 XCR1 chemokine (C motif) Down receptor 1 IL1RL1 interleukin 1 receptor- Down like 1 PIGR polymeric Down immunoglobulin receptor HFE hemochromatosis Down

(99) TABLE-US-00006 TABLE 6 Restoridyn ® (24 H after half-marathon) Significant mRNA Upregulated/ targets* ($p < 0.01$) Official Name Downregulated ZAP70 zeta-chain (TCR) Down associated protein kinase 70 kDA BTLA B and T lymphocyte Down associated CD96 CD96 molecule Down TLR5 Toll-like receptor 5 Up SELL Selectin L Up CEACAM1 Carcinoembryonic Up antigen-related cell adhesion molecule ENTPD1 Ectonucleoside Up triphosphate diphosphohydrolase 1 GNLY Granulysin Down TLR4 Toll-like receptor 4 Up STAT3 Signal transducer and Up activator of transcription 3 (acute phase response factor) KLRC4 Killer cell lectin-like Down receptor subfamily C, member 4 CD247 CD247 molecule Down CR1 Complement Up component (3b/4b) receptor 1 Knops blood group) STAT5A Signal transducer and Up activator of transcription 5A BST1 Bone marrow stromal Up cell antigen 1 CLEC5A C-type lectin domain Up family 5, member A IFI16 Interferon, gamma- Up inducible protein 16 FCGR3A/B Fo fragment of IgG, low Up affinity IIIa, receptor (CD16a)/Fc fragment of IgG, low affinity IIIb, receptor (CD16a) LILRA3 Leukocyte Up immunoglobulin-like receptor, subfamily A, member 3 LILRA2 Leukocyte Up immunoglobulin-like receptor, subfamily A, member 2 CFP Complement factor Up properdin SLAMF7 SLAM family member 7 Down MYD88 Myeloid differentiation Up primary response gene (88) TNFSF10 Tumor necrosis factor Up (ligand) superfamily, member 10 CD58 CD58 molecule Up *Top 25 targets listed

(100) TABLE-US-00007 TABLE 7 CONTROL (24 H after half-marathon) Significant mRNA Upregulated/ targets* ($p < 0.01$) Official Name Downregulated PLAUR Plasminogen activator, Up urokinase receptor FCGR3A/B Fo fragment of IgG, low Up affinity IIIa, receptor (CD16a)/Fc fragment of IgG, low affinity IIIb, receptor (CD16a) IGF2R Insulin-like growth Up factor 2

receptor LILRA3 Leukocyte Up immunoglobulin-like receptor, subfamily A, member 3 ZAP70 Zeta-chain (TCR) Down associated protein kinase 70 kDa TRAF3 TNF receptor- Down associated factor 3 BCL6 B-cell CLL/lymphoma 6 Up FCGR2A/C Fc fragment of IgG, low Up affinity IIa, receptor (CD32)/Fc fragment of IgG, low affinity IIc, receptor for (CD32) ICAM3 Intercellular adhesion Up molecule 3 IL1RN Interleukin 1 receptor Up antagonist CSF3R Colony stimulating Up factor 3 receptor (granulocyte) IL6R Interleukin 6 receptor Up HLA-B Major Up histocompatibility complex, class I, B LILRA2 Leukocyte Up immunoglobulin-like receptor, subfamily A, member 2 ENTPD1 Ectonucleoside Up triphosphate diphosphohydrolase 1 MME Membrane metallo- Up endopeptidase TNFRSF9 Tumor necrosis factor Up receptor superfamily, member 9 STAT4 Signal transducer and Down activator of transcription 4 TLR5 Toll-like receptor 5 Up TLR2 Toll-like receptor 2 Up *Top 20 targets listed

Example 3

(101) Combination Dietary Polyphenol and Methylsulfonylmethane Supplementation Alters Systemic Inflammation Time Course Response after Running a Half Marathon Race

1 Material and Methods

(102) 1.1 Participants

(103) 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.

(104) TABLE-US-00008 TABLE 8 Subject characteristics Control Treatment Gender Male = 5; Female = 5 Male = 3; Female = 2 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 Data reported as mean ± standard deviation. No significant difference between conditions.

1.2 Experimental Design

(105) 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/). Supplement safety was assessed by measuring serum alkaline phosphatase (liver function biomarker) 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).

(106) 1.3 Monitoring Exercise Training

(107) Subjects were given access to MapMyRun (UnderArmour; 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.

(108) 1.4 Biomarker Measurement

(109) 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, PAXgene 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 manufacture 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.

(110) 1.5 Statistical Analysis

(111) 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. R.sup.2 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 analyzed for significance based on a standardized fold change (1.2; $P<0.05$). Data were standardized into 6 volcano plots to identified biomarkers that were significantly up or down-regulated relative to control.

2 Results

(112) 2.1 Exercise Training

(113) 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.

(114) 2.2 Protein Biomarkers

(115) 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. **8**A “Curcumin+Pomegranate+MSM/No Supplement”; Osteonectin/SPARC, sEGFR and sIL-2Rα), 4 H (FIG. **8**B “Curcumin+Pomegranate+MSM/No Supplement”; Osteonectin/SPARC, and BDNF), and 24 H (FIG. **8**C “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.)

(116) 2.3 RNA Biomarkers

(117) 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. **10**A; PPARg & NOX1) and 24 H (FIG. **10**C; PPARg, NOX1, and CCL22) compared to control. No RNA were found to significantly increase relative to control at 4 H (FIG. **10**B). We also identified RNA that were significantly downregulated compared to control at PRE (FIG. **10**A; PACER, PTGES, MYD88, TNFS14, SOD3, THRIL, and TRAF6), 4 H (FIG. **10**B; PTGES, THRIL, MALAT1, PACER, SOD3, SATIII, CX3CL1, LNC00305), and 24 H (FIG. **10**C; 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

(118) 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 1.sup.st 24-h) because this is a critical period of time that affects the ability to return to next practice and activities of daily living.

(119) 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-2Rα). 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.

(120) 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 (PPARg, NOX1, and CCL22). Interestingly, the treatment response profile included reductions in inflammation-associated RNA, but not the corresponding proteins. Our lab and other 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.
(121) 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.
(122) 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.
(123) 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 ±10%; in other embodiments, the values may range in value above or below the stated value in a range of approximately ±5%; in other embodiments, the values may range in value above or below the stated value in a range of approximately ±2%; in other embodiments, the values may range in value above or below the stated value in a range of approximately ±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.
(124) 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.
(125) 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.
(126) TABLE-US-00009 SUPPLEMENTARY TABLE 1 Summary of Protein biomarkers Abbreviation Name Type Relevance Fractalkine Fractalkine Cytokine Inflammation GM-CSF Granulocyte macrophage Cytokine Inflammation colony-stimulating factor IFNg Interferon-gamma Cytokine Inflammation IL-10 Interleukin-10 Cytokine Inflammation IL-12p70 Interleukin-12 Cytokine Inflammation (bioactive form) 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 Cytokine Inflammation alpha chemoattractant 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 Oncostatin-M Myokine Inflammation M OSM SEGFR Soluble epidermal growth Soluble Inflammation factor receptor cytokine receptor sgp130 Soluble gp130 Soluble Inflammation cytokine receptor SIL-1RI Soluble interleukin-1 receptor, Soluble Inflammation type 1 cytokine receptor SIL-1RII Soluble interleukin-1 receptor, Soluble Inflammation type 2 cytokine receptor SIL-2Ralpha Soluble interleukin-2 receptor Soluble Inflammation subunit alpha cytokine receptor SIL-4R Soluble interleukin-4 receptor Soluble Inflammation cytokine receptor SIL-6R Soluble interleukin-6 receptor Soluble Inflammation cytokine receptor SRAGE Soluble receptor for advanced Soluble Inflammation glycation end- products cytokine receptor STNFRI Soluble tumor necrosis factor Soluble Inflammation receptor 1 cytokine receptor STNFRII Soluble tumor necrosis factor Soluble Inflammation receptor 2 cytokine receptor SVEGFR1 Soluble vascular endothelial Soluble Inflammation growth factor receptor-1 cytokine receptor SVEGFR2 Soluble vascular endothelial Soluble Inflammation growth factor receptor-2 cytokine receptor BDNF Brain-derived neurotrophic Myokine Muscle injury factor FABP3 Fatty acid-binding protein 3 Myokine Muscle injury Osteonectin/ Osteonectin/SPARC Myokine Muscle injury SPARC SVEGFR3 Soluble vascular endothelial Soluble Muscle injury growth factor receptor-3 cytokine receptor
(127) TABLE-US-00010 SUPPLEMENTARY TABLE 2 Summary of bead-based RNA biomarkers Abbreviation Name Type Pathway LINC00305 Long Intergenic Non-Protein lncRNA Inflammation Coding RNA 305 MALAT1 Metastasis associated lung lncRNA Inflammation adenocarcinoma transcript 1 NEAT1 Nuclear paraspeckle assembly lncRNA Inflammation transcript 1 NKILA NF-kappaB interacting lncRNA Inflammation lncRNA PACER P50-associated COX-2 lncRNA Inflammation extragenic RNA THRIL TNF and HNRNPL related lncRNA Inflammation immunoregulatory long non- coding RNA 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 mRNA Inflammation ligand 1 CXCL1 C-X-C motif chemokine mRNA Inflammation ligand 1 IL10 Interleukin 10 mRNA

Inflammation IL17A Interleukin 17A mRNA Inflammation IL18 Interleukin 18 mRNA Inflammation IL1B Interleukin 1 beta mRNA Inflammation IL1RN Interleukin 1 receptor mRNA Inflammation antagonist IL4 Interleukin 4 mRNA Inflammation IL6 Interleukin 6 mRNA Inflammation IL6R Interleukin 6 receptor mRNA Inflammation IL7R Interleukin 7 receptor mRNA Inflammation IL8 Interleukin 8 mRNA Inflammation MOK MOK protein kinase mRNA Inflammation MYD88 Innate immune signal mRNA Inflammation transduction adaptor MYD88 NFKB1 Nuclear factor kappa B mRNA Inflammation subunit 1 PTGES Prostaglandin E synthase mRNA Inflammation PTGS1 Prostaglandin-endoperoxide mRNA Inflammation synthase 1 PTGS2 Prostaglandin-endoperoxide mRNA Inflammation synthase 2 PTPN1 Protein tyrosine phosphatase, mRNA Inflammation non-receptor type 1 SATIII Satellite III (clone 18) mRNA Inflammation TLR2 Toll like receptor 2 mRNA Inflammation TLR4 Toll like receptor 4 mRNA Inflammation TNF Tumor necrosis factor mRNA Inflammation TNFRSF1A TNF receptor superfamily mRNA Inflammation member 1A TNFRSF1B TNF receptor superfamily mRNA Inflammation member 1B TNFSF14 TNF superfamily member 14 mRNA Inflammation TRAF6 TNF receptor associated mRNA Inflammation factor 6 VEGFC Vascular endothelial growth mRNA Muscle injury factor C GUSB Glucuronidase beta mRNA Housekeeper HPRT1 Hypoxanthine mRNA Housekeeper phosphoribosyltransferase 1 PPIB Peptidylprolyl isomerase B mRNA Housekeeper
(128) TABLE-US-00011 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 mRNA Adaptive Immune (Landsteiner-Wiener blood group) System ICAM5 intercellular adhesion molecule 5, mRNA Adaptive Immune telencephalin System KLRF1 killer cell lectin-like receptor mRNA Adaptive Immune subfamily F, member 1 System LILRA1 leukocyte immunoglobulin-like mRNA Adaptive Immune receptor, subfamily A (with TM System domain), member 1 LILRA2 leukocyte immunoglobulin-like mRNA Adaptive Immune receptor, subfamily A (with TM System domain), member 2 LILRA4 leukocyte immunoglobulin-like mRNA Adaptive Immune receptor, subfamily A (with TM System domain), member 4 LILRA5 leukocyte immunoglobulin-like mRNA Adaptive Immune receptor, subfamily A (with TM System domain), member 5 LILRB4 leukocyte immunoglobulin-like mRNA Adaptive Immune receptor, subfamily B (with TM System and ITIM domains), member 4 LILRB5 leukocyte immunoglobulin-like mRNA Adaptive Immune receptor, subfamily B (with TM System and ITIM domains), member 5 BCL2L11 BCL2-like 11 (apoptosis mRNA Apoptosis facilitator) CD82 CD82 molecule mRNA Apoptosis CRADD CASP2 and RIPK1 mRNA Apoptosis domain containing adaptor with death domain CUL9 cullin 9 mRNA Apoptosis PDCD2 programmed cell death 2 mRNA Apoptosis ATG10 ATG10 autophagy related 10 mRNA Autophagy homolog (*S. cerevisiae*) LILRB3 leukocyte immunoglobulin-like mRNA B cell Receptor receptor, subfamily B (with TM Signaling; Adaptive and ITIM domains), member 3 Immune System CD34 CD34 molecule mRNA Cell Adhesion ITGAE integrin, alpha E (antigen CD103, mRNA Cell Adhesion human mucosal lymphocyte antigen 1; alpha polypeptide) TGFBI transforming growth factor, beta- mRNA Cell Adhesion induced, 68 kDa CD22 CD22 molecule mRNA Cell Adhesion; B cell Receptor Signaling; Adaptive Immune System CCBP2 chemokine binding protein 2 mRNA Chemokine Signaling CCRL1 chemokine (C-C motif) receptor- mRNA Chemokine like 1 Signaling CCRL2 chemokine (C-C motif) receptor- mRNA Chemokine like 2 Signaling CISH cytokine inducible SH2- mRNA Cytokine containing protein Signaling CSF1R colony stimulating factor 1 mRNA Cytokine receptor Signaling CSF3R colony stimulating factor 3 mRNA Cytokine receptor (granulocyte) Signaling IL11RA interleukin 11 receptor, alpha mRNA Cytokine Signaling IL13RA1 interleukin 13 receptor, mRNA Cytokine alpha 1 Signaling IL16 interleukin 16 mRNA Cytokine Signaling IL17B interleukin 17B mRNA Cytokine Signaling IL19 interleukin 19 mRNA Cytokine Signaling 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, mRNA Cytokine alpha 2 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 mRNA Cytokine superfamily, member 17 Signaling TNFRSF8 tumor necrosis factor receptor mRNA Cytokine superfamily, member 8 Signaling TNFSF12 tumor necrosis factor (ligand) mRNA Cytokine superfamily, member 12 Signaling TNFSF15 tumor necrosis factor (ligand) mRNA Cytokine superfamily, member 15 Signaling CCL11 chemokine (C-C motif) ligand 11 mRNA Cytokine Signaling; Chemokine Signaling CCL15 chemokine (C-C motif) ligand 15 mRNA Cytokine Signaling; Chemokine Signaling CCL16 chemokine (C-C motif) ligand 16 mRNA Cytokine Signaling; Chemokine Signaling CCL18 chemokine (C-C motif) ligand 18 mRNA Cytokine (pulmonary and activation- Signaling; Chemokine regulated) Signaling CCL22 chemokine (C-C motif) ligand 22 mRNA Cytokine Signaling; Chemokine Signaling CCL23 chemokine (C-C motif) ligand 23 mRNA Cytokine Signaling; Chemokine Signaling CCL24 chemokine (C-C motif) ligand 24 mRNA Cytokine Signaling; Chemokine Signaling CCL26 chemokine (C-C motif) ligand 26 mRNA Cytokine Signaling; Chemokine Signaling CCL7 chemokine (C-C motif) ligand 7 mRNA Cytokine Signaling; Chemokine Signaling CCL8 chemokine (C-C motif) ligand 8 mRNA Cytokine Signaling; Chemokine Signaling CCR1 chemokine (C-C motif) receptor 1 mRNA Cytokine Signaling; Chemokine Signaling CCR10 chemokine (C-C motif) receptor 10 mRNA Cytokine Signaling; Chemokine Signaling CCR8 chemokine (C-C motif) receptor 8 mRNA Cytokine Signaling; Chemokine Signaling CX3CR1 chemokine (C-X3-C motif) mRNA Cytokine receptor 1 Signaling; Chemokine Signaling CXCL13 chemokine (C-X-C motif) ligand mRNA Cytokine 13 Signaling; Chemokine Signaling CXCR3 chemokine (C-X-C motif) receptor 3 mRNA Cytokine Signaling; Chemokine Signaling CXCR6 chemokine (C-X-C motif) receptor 6 mRNA Cytokine Signaling; Chemokine Signaling XCR1 chemokine (C motif) receptor 1 mRNA Cytokine Signaling; Chemokine Signaling CD9 CD9 molecule mRNA Hemostasis EDNRB endothelin receptor type B mRNA Hemostasis FCGRT Fc fragment of IgG, receptor, mRNA Hemostasis transporter, alpha GP1BB glycoprotein Ib (platelet), beta mRNA Hemostasis polypeptide HAMP hepcidin antimicrobial peptide mRNA Hemostasis CSF2RB colony stimulating factor 2 mRNA Hemostasis; receptor, beta, low-affinity Cytokine (granulocyte-macrophage) Signaling; Apoptosis IL3 interleukin 3 (colony-stimulating mRNA Hemostasis; factor, multiple) Cytokine Signaling; Apoptosis C14orf166 chromosome 14 open reading mRNA Host-pathogen frame 166 Interaction CD3EAP CD3e molecule, epsilon associated mRNA Host-pathogen protein Interaction IRGM immunity-related GTPase family, M mRNA Host-pathogen Interaction KLRB1 Killer cell lectin-like receptor mRNA Host-pathogen subfamily B, member I Interaction; Adaptive Immune System MASP2 Mannan-binding lectin serine mRNA Host-pathogen peptidase 2 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 mRNA Host-pathogen glycoprotein IIb of IIb/IIIa Interaction; complex, antigen CD41) Hemostasis ITGA6 Integrin, alpha 6 mRNA Host-pathogen Interaction; Hemostasis; Cell Adhesion SELPLG Selectin P ligand mRNA Host-pathogen Interaction; Hemostasis; Cell Adhesion C1QBP Complement component 1, q mRNA Host-pathogen subcomponent binding protein Interaction; Hemostasis; Complement System PDGFB Platelet-derived growth factor beta mRNA Host-pathogen polypeptide Interaction; Hemostasis; Cytokine Signaling ABCF1 ATP-binding cassette, sub-family mRNA Housekeeper F (GCN20), member 1 ALAS1 Aminolevulinate, delta-,synthase 1 mRNA Housekeeper EEF1G Eukaryotic translation elongation mRNA Housekeeper factor 1 gamma G6PD Glucose-6-phosphate mRNA Housekeeper dehydrogenase GAPDH Glyceraldehyde-3-phosphate mRNA Housekeeper dehydrogenase GUSB Glucuronidase, beta mRNA Housekeeper HPRT1 Hypoxanthine mRNA

Housekeeper phosphoribosyltransferase 1 OAZ1 Ornithine decarboxylase antizyme 1 mRNA Housekeeper POLR1B Polymerase (RNA) I polypeptide mRNA Housekeeper B, 128 kDa POLR2A Polymerase (RNA) II (DNA mRNA Housekeeper directed) polypeptide A, 220 kDa PPIA Peptidylprolyl isomerase A mRNA Housekeeper (cyclophilin A) RPL19 Ribosomal protein L19 mRNA Housekeeper SDHA Succinate dehydrogenase complex, mRNA Housekeeper subunit A, flavoprotein (Fp) TBP TATA box binding protein mRNA Housekeeper TUBB Tubulin, beta mRNA Housekeeper KLRAP1 Killer cell lectin-like receptor mRNA Immune System subfamily A pseudogene 1 ABCB1 ATP-binding cassette, sub-family mRNA Immunometabolism B (MDR/TAP), member 1 B3GAT1 Beta-1,3-glucuronyltransferase 1 mRNA Immunometabolism (glucuronosyltransferase P) CMKLR1 Chemokine-like receptor 1 mRNA Immunometabolism FKBP5 FK506 binding protein 5 mRNA Immunometabolism KCNJ2 Potassium inwardly- rectifying mRNA Immunometabolism channel, subfamily J, member 2 LTB4R Leukotriene B4 receptor mRNA Immunometabolism LTB4R2 Leukotriene B4 receptor 2 mRNA Immunometabolism NT5E 5'-nucleotidase, ecto (CD73) mRNA Immunometabolism PLA2G2E Phospholipase A2, group IIE mRNA Immunometabolism RARRES3 Retinoic acid receptor responder mRNA Immunometabolism (tazarotene induced) 3 ARG2 Arginase, type II mRNA Immunometabolism; Host-pathogen interaction ENTPD1 Ectonucleoside triphosphate mRNA Immunometabolism; diphosphohydrolase 1 Host-pathogen interaction SLC2A1 Solute carrier family 2 (facilitated mRNA Immunometabolism; glucose transporter), member 1 Host-pathogen interaction CD53 CD53 molecule mRNA Innate Immune System CD97 CD97 molecule mRNA Innate Immune System CLEC4A C-type lectin domain family 4, mRNA Innate Immune member A System CLEC5A C-type lectin domain family 5, mRNA Innate Immune member A System CLEC6A C-type lectin domain family 6, mRNA Innate Immune member A 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 mRNA Innate Immune 1, receptor for; alpha polypeptide 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 mRNA Innate Immune receptor System TNFAIP6 tumor necrosis factor, alpha- mRNA Innate Immune induced protein 6 System LAIR1 leukocyte-associated mRNA Innate Immune immunoglobulin- like receptor 1 System; Adaptive Immune System LILRA3 leukocyte immunoglobulin-like mRNA Innate Immune receptor, subfamily A (without System; Adaptive TM domain), member 3 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 mRNA Innate Immune cell adhesion molecule 6 (non- System; Hemostasis specific cross reacting antigen) CEACAM8 carcinoembryonic antigen-related mRNA Innate Immune cell adhesion molecule 8 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 mRNA Innate Immune receptor System; Hemostasis; Complement System PPBP pro- platelet basic protein mRNA Innate Immune (chemokine (C-X-C motif) ligand 7) System; Hemostasis; Cytokine Signaling; Chemokine Signaling IFIH1 interferon induced with helicase C

mRNA Innate Immune domain 1 System; Host- pathogen Interaction C1QA complement component 1, q mRNA Innate Immune subcomponent, A chain System; Host- pathogen Interaction; Complement System C1QB complement component 1, q mRNA Innate Immune subcomponent, B chain System; Host- pathogen Interaction; Complement System C1S complement component 1, s mRNA Innate Immune subcomponent System; Host- pathogen Interaction; Complement System C2 complement component 2 mRNA Innate Immune System; Host- pathogen Interaction; Complement System C4A/B complement component 4A mRNA Innate Immune (Rodgers blood System; Host- group)/complement component 4B pathogen (Chido blood group) Interaction; Complement System C4BPA complement component 4 binding mRNA Innate Immune protein, alpha System; Host- pathogen Interaction; Complement System C5 complement component 5 mRNA Innate Immune System; Host- pathogen Interaction; Complement System C8A complement component 8, alpha mRNA Innate Immune polypeptide System; Host- pathogen Interaction; Complement System C8B complement component 8, beta mRNA Innate Immune polypeptide System; Host- pathogen Interaction; Complement System C8G complement component 8, gamma mRNA Innate Immune polypeptide 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) mRNA Innate Immune receptor 1 (Knops blood group) System; Host- pathogen Interaction; Complement System MASP1 mannan-binding lectin serine mRNA Innate Immune peptidase 1 (C4/C2 activating System; Host- component of Ra-reactive factor) 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 System; B cell Receptor Signaling; Adaptive Immune System CD58 CD58 molecule mRNA 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 mRNA Innate Immune (C1 inhibitor), member 1 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 mRNA Innate Immune component 3 receptor 4 subunit) System; Host- pathogen Interaction; Hemostasis; Cytokine Signaling; Complement System; Cell Adhesion GPI glucose-6-phosphate isomerase mRNA Innate Immune System; Immuno- metabolism PLA2G2A phospholipase A2, group IIA mRNA Innate Immune (platelets, synovial fluid) System; Immuno- metabolism AICDA activation-induced cytidine mRNA Lymphocyte deaminase 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 mRNA Lymphocyte subfamily C, member 3 Activation KLRC4 killer cell lectin-like receptor mRNA Lymphocyte subfamily C, member 4 Activation KLRF2 killer cell lectin-like receptor mRNA Lymphocyte subfamily F, member 2 Activation KLRG2 killer cell lectin-like receptor mRNA Lymphocyte subfamily G, member 2 Activation LILRB2 leukocyte immunoglobulin-like mRNA Lymphocyte receptor, subfamily B (with TM Activation and ITIM domains), member 2 MS4A1 membrane-spanning 4-domains, mRNA Lymphocyte subfamily A, member 1 Activation PRDM1 PR domain containing 1, with mRNA Lymphocyte ZNF domain

Activation BTLA B and T lymphocyte associated mRNA Lymphocyte Activation; Adaptive Immune System KIR_Inhibiting_Sub- killer cell immunoglobulin-like mRNA Lymphocyte group_1 receptor Activation; Adaptive Immune System KIR_Inhibiting_Sub- killer cell immunoglobulin-like mRNA Lymphocyte group_2 receptor Activation; Adaptive Immune System KIR3DL1 killer cell immunoglobulin-like mRNA Lymphocyte receptor, three domains, long Activation; Adaptive cytoplasmic tail, 1 Immune System KIR3DL2 killer cell immunoglobulin-like mRNA Lymphocyte receptor, three domains, long Activation; Adaptive cytoplasmic tail, 2 Immune System KIR3DL3 killer cell immunoglobulin-like mRNA Lymphocyte receptor, three domains, long Activation; Adaptive cytoplasmic tail, 3 Immune System KLRC1 killer cell lectin-like receptor mRNA Lymphocyte subfamily C, member 1 Activation; Adaptive Immune System KLRG1 killer cell lectin-like receptor mRNA Lymphocyte subfamily G, member 1 Activation; Adaptive Immune System LILRB1 leukocyte immunoglobulin-like mRNA Lymphocyte receptor, subfamily B (with TM Activation; Adaptive and ITIM domains), member 1 Immune System NCR1 natural cytotoxicity triggering mRNA Lymphocyte receptor 1 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, mRNA Lymphocyte cytotoxic T-lymphocyte- Activation; Apoptosis associated serine esterase 3) GZMB granzyme B (granzyme 2, mRNA Lymphocyte cytotoxic T-lymphocyte- Activation; Apoptosis associated serine esterase 1) GZMK granzyme K (granzyme 3; tryptase mRNA Lymphocyte II) Activation; Apoptosis PRF1 perforin 1 (pore forming protein) mRNA Lymphocyte Activation; Apoptosis CD79A CD79a molecule, mRNA Lymphocyte immunoglobulin-associated alpha Activation; B cell Receptor Signaling; Adaptive Immune System CD79B CD79b molecule, mRNA Lymphocyte immunoglobulin-associated beta 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 mRNA Lymphocyte ITIM domains Activation; Cell Adhesion CD274 CD274 molecule mRNA Lymphocyte Activation; Cell Adhesion; Adaptive Immune System ICOSLG inducible T-cell co-stimulator mRNA Lymphocyte ligand 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, mRNA Lymphocyte lambda 2) Activation; Cytokine Signaling IL28A/B interleukin 28A (interferon, mRNA Lymphocyte lambda 2)/interleukin 28B Activation; Cytokine (interferon, lambda 3) Signaling IL29 interleukin 29 (interferon, mRNA Lymphocyte lambda 1) 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 mRNA Lymphocyte sarcoma viral oncogene homolog Activation; Cytokine Signaling PTPN2 protein tyrosine phosphatase, non- mRNA Lymphocyte receptor type 2 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 mRNA Lymphocyte superfamily, member 13B Activation; Cytokine Signaling TNFRSF4 tumor necrosis factor receptor mRNA Lymphocyte superfamily, member 4 Activation; Cytokine Signaling TNFRSF9 tumor necrosis factor receptor mRNA Lymphocyte superfamily, member 9 Activation; Cytokine Signaling TNFSF4 tumor necrosis factor (ligand) mRNA Lymphocyte superfamily, member 4 Activation;

Cytokine Signaling TNFSF8 tumor necrosis factor (ligand) mRNA Lymphocyte superfamily, member 8 Activation; Cytokine Signaling XCL1 chemokine (C motif) ligand 1 mRNA Lymphocyte Activation; Cytokine Signaling; Chemokine Signaling CD244 CD244 molecule, natural killer mRNA Lymphocyte cell receptor 2B4 Activation; Hemostasis CD48 CD48 molecule mRNA Lymphocyte Activation; Hemostasis CD2 CD2 molecule mRNA Lymphocyte Activation; Hemostasis; Cell Adhesion KLRK1 killer cell lectin-like receptor mRNA Lymphocyte subfamily K, member 1 Activation; Host- pathogen Interaction PTGER4 prostaglandin E receptor 4 mRNA Lymphocyte (subtype EP4) Activation; Host- pathogen Interaction SLAMF1 signaling lymphocytic activation mRNA Lymphocyte molecule family member 1 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 mRNA Lymphocyte agonist Activation; Host- pathogen Interaction; Apoptosis CCND3 cyclin D3 mRNA Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling CDKN1A cyclin-dependent kinase inhibitor mRNA Lymphocyte 1A (p21, Cip1) Activation; Host- pathogen Interaction; Cytokine Signaling TNFRSF14 tumor necrosis factor receptor mRNA Lymphocyte superfamily, member 14 Activation; Host- pathogen Interaction; Cytokine Signaling; Adaptive Immune System TNFRSF10C tumor necrosis factor receptor mRNA Lymphocyte superfamily, member 10c, decoy Activation; Host- without an intracellular domain pathogen Interaction; Cytokine Signaling; Apoptosis IDO1 indoleamine 2,3- mRNA Lymphocyte dioxygenase 1 Activation; Immuno- metabolism; Host- pathogen Interaction KIR_Activating_Sub- killer cell immunoglobulin-like mRNA Lymphocyte group_1 receptor Activation; Innate Immune System KLRC2 killer cell lectin-like receptor mRNA Lymphocyte subfamily C, member 2 Activation; Innate Immune System LGALS3 lectin, galactoside-binding, mRNA Lymphocyte soluble, 3 Activation; Innate Immune System KIR_Activating_Sub- killer cell immunoglobulin-like mRNA Lymphocyte group_2 receptor Activation; Innate Immune System; Adaptive Immune System KLRD1 killer cell lectin-like receptor mRNA Lymphocyte subfamily D, member 1 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 mRNA Lymphocyte accelerating factor for complement Activation; Innate (Cromer blood group) Immune System; Complement System CD59 CD59 molecule, complement mRNA Lymphocyte regulatory protein 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 mRNA Lymphocyte cell adhesion molecule 1 (biliary Activation; Innate glycoprotein) Immune System; Hemostasis MIF macrophage migration inhibitory mRNA Lymphocyte factor (glycosylation-inhibiting Activation; Innate factor) Immune System; Hemostasis; Cytokine Signaling CLEC4E C-type lectin domain family 4, mRNA Lymphocyte member E Activation; Innate Immune System; Host- pathogen Interaction CD46 CD46 molecule, complement mRNA Lymphocyte regulatory protein Activation; Innate Immune System; Host-pathogen Interaction; Complement System CR2 complement component mRNA Lymphocyte (3d/Epstein Barr virus) receptor 2 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 FCER1G Fc fragment of IgE, high affinity I, mRNA Lymphocyte receptor for; gamma polypeptide 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 ARHGDIB Rho GDP dissociation inhibitor mRNA Lymphocyte (GDI) beta

Trafficking; Apoptosis CDH5 cadherin 5, type 2 (vascular mRNA Lymphocyte endothelium) 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 mRNA Lymphocyte molecule 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, mRNA Lymphocyte alpha 4 subunit of VLA-4 Trafficking; Lymphocyte receptor) Activation; Host- pathogen Interaction; Hemostasis; Cell Adhesion; Adaptive Immune System CTNNB1 catenin (cadherin-associated mRNA Lymphocyte protein), beta 1, 88 kDa Trafficking; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction ITGAL integrin, alpha L (antigen CD11A mRNA Lymphocyte (p180), Trafficking; Lymphocyte lymphocyte function-associated Activation; Innate antigen 1; alpha polypeptide) Immune System; Host- pathogen Interaction; Hemostasis; Cell Adhesion; Adaptive Immune System MR1 major histocompatibility complex, mRNA MHC Class I class I-related Antigen Presentation LILRA6 leukocyte immunoglobulin-like mRNA MHC Class I receptor, subfamily A (with TM Antigen domain), member 6 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 mRNA MHC Class I homolog (*S. cerevisiae*) Antigen Presentation; Innate Immune System; Autophagy; Adaptive Immune System ZBTB16 zinc finger and BTB domain mRNA MHC Class I containing 16 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 mRNA MHC Class II histocompatibility complex, class Antigen II invariant chain Presentation; Lymphocyte Activation; Host- pathogen Interaction; Hemostasis; Adaptive Immune System IKBKAP inhibitor of kappa light mRNA NF-kB Signaling polypeptide gene enhancer in B-cells, kinase complex-associated protein TAGAP T-cell activation RhoGTPase mRNA NF-kB Signaling activating protein TNFRSF11A tumor necrosis factor receptor mRNA NF-kB superfamily, member 11a, NFKB Signaling; Cytokine activator Signaling CCL13 chemokine (C-C motif) ligand 13 mRNA NF-kB Signaling; Cytokine Signaling; Chemokine Signaling LTBR lymphotoxin beta receptor (TNFR mRNA NF-kB superfamily, member 3) Signaling; Host-pathogen Interaction; Cytokine Signaling PLAU plasminogen activator, urokinase mRNA NF-kB Signaling; Innate Immune System; Hemostasis; Complement System TNFSF11 tumor necrosis factor (ligand) mRNA NF-kB superfamily, member 11 Signaling; Lymphocyte Activation; Cytokine Signaling TNFSF13B tumor necrosis factor (ligand) mRNA NF-kB superfamily, member 13b Signaling; Lymphocyte Activation; Cytokine Signaling 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 mRNA NF-kB superfamily, member 13C 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 mRNA NLR (*S. cerevisiae*) signaling; Autophagy IFI16 interferon, gamma-inducible mRNA NLR protein 16 signaling; Innate Immune System

CASP2 caspase 2, apoptosis-related mRNA NLR cysteine peptidase signaling; Innate Immune System; Apoptosis ATG12 ATG12 autophagy related 12 mRNA NLR homolog (*S. cerevisiae*) signaling; Innate Immune System; Autophagy CAMP cathelicidin antimicrobial peptide mRNA NLR signaling; Innate Immune System; Host- pathogen Interaction CARD9 caspase recruitment domain mRNA NLR family, member 9 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 mRNA NLR cysteine peptidase (interleukin 1, signaling; Innate beta, convertase) Immune System; Inflammasomes; Host-pathogen Interaction; Cytokine Signaling IL18 interleukin 18 (interferon-gamma- mRNA NLR inducing factor) signaling; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling ATG5 ATG5 autophagy related 5 mRNA NLR homolog (*S. cerevisiae*) signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Autophagy NLRP3 NLR family, pyrin domain mRNA NLR containing 3 signaling; Lymphocyte Activation; Innate Immune System; Inflammasomes; Host- pathogen Interaction PYCARD PYD and CARD domain mRNA NLR containing signaling; Lymphocyte Activation; Innate Immune System; Inflammasomes; Host-pathogen Interaction IL18RAP interleukin 18 receptor accessory mRNA Oxidative protein Stress; Cytokine Signaling MCL1 myeloid cell leukemia sequence 1 mRNA Oxidative (BCL2-related) Stress; Cytokine Signaling; Apoptosis PDGFRB platelet-derived growth factor mRNA Oxidative receptor, beta polypeptide 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 mRNA Oxidative A-2) viral oncogene homolog Stress; Lymphocyte (avian) Activation; Host- pathogen Interaction; Chemokine Signaling ADA adenosine deaminase mRNA Oxidative Stress; Lymphocyte Activation; Immuno- metabolism ABL1 c-abl oncogene 1, non-receptor mRNA Oxidative tyrosine kinase Stress; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Hemostasis CCL19 chemokine (C-C motif) ligand 19 mRNA Oxidative Stress; NF-kB Signaling; Lymphocyte Activation; Cytokine Signaling; Chemokine Signaling BCL2 B-cell CLL/lymphoma 2 mRNA Oxidative Stress; NLR signaling; NF-kB 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 mRNA Phagocytosis and protein 3 Degradation LITAF lipopolysaccharide-induced TNF mRNA Phagocytosis and factor Degradation MARCO macrophage receptor with mRNA Phagocytosis and collagenous structure 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 mRNA Phagocytosis and IIa, receptor (CD32)/Fc fragment Degradation; Host- of IgG, low affinity IIc, receptor pathogen for (CD32) Interaction FCGR2B Fc fragment of IgG, low affinity mRNA Phagocytosis and IIb, receptor (CD32) Degradation; Host- pathogen Interaction; B cell Receptor Signaling; Adaptive Immune System ITGA5 integrin, alpha 5 (fibronectin mRNA Phagocytosis and receptor, alpha polypeptide) Degradation; Host- pathogen Interaction; Hemostasis IGF2R insulin-like growth factor 2 mRNA Phagocytosis and receptor 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 mRNA Phagocytosis and IIa, receptor (CD32) Degradation; Innate Immune System; Host- pathogen Interaction C1R complement component 1, r mRNA Phagocytosis and subcomponent Degradation; Innate Immune System; Host- pathogen Interaction; Complement System 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, mRNA Phagocytosis and member A Degradation; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction FCGR3A/B Fc fragment of IgG, low affinity mRNA Phagocytosis and IIIa, receptor (CD16a)/Fc Degradation; Lymphocyte fragment of IgG, low affinity IIIb, Activation; Innate receptor (CD16a) 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 mRNA Phagocytosis and receptor, beta polypeptide, antigen Degradation; Lymphocyte CD29 includes MDF2, MSK12) 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 mRNA Phagocytosis and cassette, sub-family B Degradation; MHC (MDR/TAP) Class I Antigen Presentation; Host- pathogen Interaction; Adaptive Immune System TAP2 transporter 2, ATP-binding mRNA Phagocytosis and cassette, sub-family B Degradation; MHC (MDR/TAP) Class I Antigen Presentation; Host- pathogen Interaction; Adaptive Immune System NCF4 neutrophil cytosolic factor 4, mRNA Phagocytosis and 40 kDa Degradation; MHC Class I Antigen Presentation; Lymphocyte Trafficking; Innate Immune System; Host- pathogen Interaction; Adaptive Immune System HLA-DMA major histocompatibility complex, mRNA Phagocytosis and class II, DM alpha Degradation; MHC Class II Antigen Presentation; Host- pathogen Interaction; Cell Adhesion HLA-DOB major histocompatibility complex, mRNA Phagocytosis and class II, DO beta 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, mRNA Phagocytosis and class II, DM beta Degradation; MHC Class II Antigen Presentation; Lymphocyte Activation; Host- pathogen Interaction; Cell Adhesion; Adaptive Immune System MBL2 mannose-binding lectin (protein C) mRNA Phagocytosis and 2, soluble Degradation; Oxidative Stress; Innate Immune System; Host- pathogen Interaction; Complement System CYBB cytochrome b-245, beta mRNA Phagocytosis and polypeptide Degradation; Oxid ative Stress; NLR signaling; MHC Class I Antigen Presentation; Lymphocyte Trafficking; Innate Immune System; Host- pathogen Interaction; Adaptive Immune System PTPN22 protein tyrosine phosphatase, non- mRNA T Cell Receptor receptor type 22 (lymphoid) 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 CTLA4_all cytotoxic T-lymphocyte- mRNA T Cell Receptor associated protein 4 Signaling; Lymphocyte Activation; Cell Adhesion; Adaptive Immune System CTLA4-TM cytotoxic T-lymphocyte- mRNA T Cell Receptor associated protein 4 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- mRNA T Cell Receptor associated protein 4 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 mRNA T Cell Receptor complex) Signaling; Lymphocyte Activation; Host- pathogen Interaction; Adaptive Immune System CD3E CD3e molecule, epsilon (CD3-mRNA T Cell Receptor TCR complex) 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

CD45R0 protein tyrosine phosphatase, mRNA T Cell Receptor receptor type, C Signaling; Lymphocyte Activation; Innate Immune System; Cell Adhesion; Adaptive Immune System CD45RA protein tyrosine phosphatase, mRNA T Cell Receptor receptor type, C Signaling; Lymphocyte Activation; Innate Immune System; Cell Adhesion; Adaptive Immune System CD45RB protein tyrosine phosphatase, mRNA T Cell Receptor receptor type, C Signaling; Lymphocyte Activation; Innate Immune System; Cell Adhesion; Adaptive Immune System PTPRC_all protein tyrosine phosphatase, mRNA T Cell Receptor receptor type, C Signaling; Lymphocyte Activation; Innate Immune System; Cell Adhesion; Adaptive Immune System 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 mRNA T Cell Receptor (SH2 domain containing leukocyte Signaling; Lymphocyte protein of 76 kDa) Activation; Innate Immune System; Hemostasis; Adaptive Immune System FYN FYN oncogene related to SRC, mRNA T Cell Receptor FGR, YES 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 mRNA T Cell Receptor oncogene homolog 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 mRNA T Cell Receptor oncogene homolog 1 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 mRNA T Cell Receptor protein kinase 70 kDa Signaling; NF-kB Signaling; Lymphocyte Activation; Adaptive Immune System CD40LG CD40 ligand mRNA T Cell Receptor Signaling; NF-kB 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-kB Signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; B cell Receptor Signaling; Adaptive Immune System MALT1 mucosa associated lymphoid tissue mRNA T Cell Receptor lymphoma translocation gene 1 Signaling; NF-kB Signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; B cell Receptor Signaling; Adaptive Immune System LCK lymphocyte-specific protein mRNA T Cell Receptor tyrosine kinase Signaling; NF-kB Signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Hemostasis; Cytokine Signaling; Adaptive Immune System PSMB7 proteasome (prosome, macropain) mRNA T Cell Receptor subunit, beta type, 7 Signaling; NF-kB 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) mRNA T Cell Receptor subunit, beta type, 9 (large Signaling; NF-kB multifunctional peptidase 2) 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) mRNA T Cell Receptor 26S subunit, ATPase, 2 Signaling; NF-kB 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) mRNA T Cell Receptor 26S subunit, non-ATPase, 7 Signaling; NF-kB Signaling; MHC Class I Antigen Presentation; Innate Immune System; Immuno- metabolism; Host- pathogen Interaction; Cytokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System PSMB10 proteasome (prosome, macropain) mRNA T Cell Receptor subunit, beta type, 10 Signaling; NF-kB 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) mRNA T Cell Receptor subunit, beta type, 5 Signaling; Oxidative Stress; NF-kB 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 mRNA TGF-b Signaling homolog (avian) SMAD5 SMAD family member 5 mRNA TGF-b Signaling IL17A interleukin 17A mRNA Th17 Differentiation; Cytokine Signaling IL17F interleukin 17F mRNA Th17 Differentiation; Cytokine Signaling IL1RAP interleukin 1 receptor accessory mRNA Th17 protein 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 mRNA Th17 (gp130, oncostatin M receptor) Differentiation; Lymphocyte Activation; Cytokine Signaling 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, mRNA Th17 beta 1 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 mRNA Th2 factor, eosinophil) 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 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 mRNA TLR 11 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 mRNA TLR kinase 3 Signaling; Innate Immune System; Cytokine Signaling SIGIRR single immunoglobulin and toll- mRNA TLR interleukin 1 receptor (TIR) Signaling; Innate domain Immune System; Cytokine Signaling TOLLIP toll interacting protein mRNA TLR Signaling; Innate Immune System; Cytokine Signaling 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- mRNA TLR activated protein kinase 2 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-kB Signaling; Host-pathogen Interaction; Cytokine Signaling; Chemokine Signaling CD40 CD40 molecule, TNF receptor mRNA TLR superfamily member 5 Signaling; NF-kB Signaling; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling; Cell Adhesion 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 mRNA TLR tyrosine kinase 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) mRNA TLR domain containing adaptor protein 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 mRNA TLR polypeptide gene enhancer in B- Signaling; NLR cells, kinase epsilon signaling; Innate Immune System; Host- pathogen Interaction IRAK2 interleukin-1 receptor-associated mRNA TLR kinase 2 Signaling; NLR signaling; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling NOD1 nucleotide-binding mRNA TLR oligomerization domain containing Signaling; NLR 1 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 IRAK1 interleukin-1 receptor-associated mRNA TLR kinase 1 Signaling; NLR signaling; NF-kB Signaling; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling IRAK4 interleukin-1 receptor-associated mRNA TLR kinase 4 Signaling; NLR signaling; NF-kB Signaling; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling TICAM1 toll-like receptor adaptor molecule mRNA TLR 1 Signaling; NLR signaling; NF-kB Signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Apoptosis MYD88 myeloid differentiation primary mRNA TLR response gene (88) 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 mRNA TLR protein Signaling; Oxidative Stress; NLR signaling; Innate Immune System; Inflammasomes; Hemostasis; Cytokine Signaling ITGAM integrin, alpha M (complement mRNA TLR component 3 receptor 3 subunit) Signaling; Phagocytosis and Degradation; Lymphocyte Trafficking; Innate Immune System; Host- pathogen Interaction; Hemostasis; Cytokine Signaling; Complement System; Cell Adhesion ITGB2 integrin, beta 2 (complement mRNA TLR component 3 receptor 3 and 4 Signaling; Phagocytosis and subunit) Degradation; Lymphocyte Trafficking; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Hemostasis; Cytokine Signaling; Complement System; Cell Adhesion; Adaptive Immune System 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-kB 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-kB Signaling; MHC Class I Antigen

Presentation; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Apoptosis; Adaptive Immune System CD36 CD36 molecule (thrombospondin mRNA TLR receptor) 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-kB Signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling; Autophagy; Adaptive Immune System IL12A interleukin 12A (natural killer cell mRNA TLR stimulatory factor 1, cytotoxic Signaling; Th1 lymphocyte maturation factor 1, Differentiation; Lymphocyte p35) Activation; Host- pathogen Interaction; Cytokine Signaling IL12B interleukin 12B (natural killer cell mRNA TLR stimulatory factor 2, cytotoxic Signaling; Th17 lymphocyte maturation factor 2, Differentiation; Th1 p40) Differentiation; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling CXCL10 chemokine (C-X-C motif) ligand mRNA TLR 10 Signaling; TNF Family Signaling; Host- pathogen Interaction; Cytokine Signaling; Chemokine Signaling CASP8 caspase 8, apoptosis-related mRNA TLR cysteine peptidase Signaling; TNF Family Signaling; NLR signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Apoptosis FADD Fas (TNFRSF6)- mRNA TLR associated via death domain Signaling; TNF Family Signaling; NLR signaling; Lymphocyte Activation; Innate Immune System; Host-pathogen Interaction; Apoptosis NOD2 nucleotide-binding mRNA TLR oligomerization domain containing Signaling; TNF 2 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-kB Signaling; Innate Immune System; Host- pathogen Interaction; Cytoki ne 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; Chemokine Signaling IKBKB inhibitor of kappa light mRNA TLR polypeptide gene enhancer in B- Signaling; TNF cells, kinase beta 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 mRNA TLR polypeptide gene enhancer in B- Signaling; TNF cells, kinase gamma 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 mRNA TLR ubiquitous kinase 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; Cytokine Signaling; Chemokine Signaling; B cell Receptor Signaling; Autophagy; Apoptosis IL1B interleukin 1, beta mRNA 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 mRNA TLR 11 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 mRNA TLR 14 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-b Signaling; T Cell Receptor

Signaling; Oxidative Stress; NLR signaling; NF-kB Signaling; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Apoptosis IL6 interleukin 6 (interferon, mRNA TLR beta 2) Signaling; TNF Family Signaling; Th2 Differentiation; Th17 Differentiation; Oxidative Stress; NLR signaling; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling MAP4K1 mitogen-activated protein kinase mRNA TNF Family kinase kinase kinase 1 Signaling MAP4K2 mitogen-activated protein kinase mRNA TNF Family kinase kinase kinase 2 Signaling MAP4K4 mitogen-activated protein kinase mRNA TNF Family kinase kinase kinase 4 Signaling CSF1 colony stimulating factor 1 mRNA TNF Family (macrophage) Signaling; Cytokine Signaling LIF leukemia inhibitory factor mRNA TNF Family (cholinergic differentiation factor) 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 mRNA TNF Family 1 Signaling; Cytokine Signaling; Chemokine Signaling SELE selectin E mRNA TNF Family Signaling; Host- pathogen Interaction; Hemostasis; Cell Adhesion TNFRSF1B tumor necrosis factor receptor mRNA TNF Family superfamily, member 1B Signaling; Innate Immune System; Cytokine Signaling CASP10 caspase 10, apoptosis-related mRNA TNF Family cysteine peptidase 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) mRNA TNF Family superfamily, member 10 Signaling; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling; Apoptosis TRAF4 TNF receptor-associated factor 4 mRNA TNF Family Signaling; NF-kB Signaling TRAF1 TNF receptor-associated factor 1 mRNA TNF Family Signaling; NF-kB Signaling; Host- pathogen Interaction; Apoptosis LTA lymphotoxin alpha (TNF mRNA TNF Family superfamily, member 1) Signaling; NF-kB Signaling; Host- pathogen Interaction; Cytokine Signaling CXCL1 chemokine (C-X-C motif) ligand 1 mRNA TNF Family (melanoma growth stimulating Signaling; NLR activity, alpha) signaling; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling; Chemokine Signaling CCL2 chemokine (C-C motif) ligand 2 mRNA 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 mRNA TNF Family cysteine peptidase Signaling; Oxidative Stress; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling; Apoptosis FAS Fas (TNF receptor superfamily, mRNA TNF Family member 6) Signaling; Oxidative Stress; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling; Apoptosis PTGS2 prostaglandin-endoperoxide mRNA TNF Family synthase 2 (prostaglandin G/H Signaling; Oxidative synthase and cyclooxygenase) Stress; NF-KB Signaling; Immuno- metabolism; Host-pathogen Interaction; Cytokine Signaling TNFAIP3 tumor necrosis factor, alpha- mRNA TNF Family induced protein 3 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 mRNA TNF Family (granulocyte-macrophage) Signaling; T Cell Receptor Signaling; Lymphocyte Activation; Host- pathogen Interaction; Hemostasis; Cytokine Signaling BATF3 basic leucine zipper transcription mRNA Transcriptional factor, ATF-like 3 Regulation GFI1 growth factor independent 1 mRNA Transcriptional transcription repressor Regulation IKZF2 IKAROS family zinc finger 2 mRNA Transcriptional (Helios) Regulation ILF3 interleukin enhancer binding factor mRNA Transcriptional 3, 90 kDa Regulation NFIL3 nuclear factor, interleukin 3 mRNA Transcriptional

regulated Regulation NFKBIZ nuclear factor of kappa light mRNA Transcriptional polypeptide gene enhancer in B- Regulation cells inhibitor, zeta PAX5 paired box 5 mRNA Transcriptional Regulation RUNX1 runt-related transcription factor 1 mRNA Transcriptional Regulation TAL1 T-cell acute lymphocytic leukemia mRNA Transcriptional 1 Regulation TCF4 transcription factor 4 mRNA Transcriptional Regulation EGR2 early growth response 2 mRNA Transcriptional Regulation; Host- pathogen Interaction PPARG peroxisome proliferator-activated mRNA Transcriptional receptor gamma Regulation; Immuno- metabolism EOMES eomesodermin mRNA Transcriptional Regulation; Lymphocyte Activation IKZF1 IKAROS family zinc finger 1 mRNA Transcriptional (Ikaros) Regulation; Lymphocyte Activation IKZF3 IKAROS family zinc finger 3 mRNA Transcriptional (Aiolos) Regulation; Lymphocyte Activation LEF1 lymphoid enhancer-binding factor mRNA Transcriptional 1 Regulation; Lymphocyte Activation POU2F2 POU class 2 homeobox 2 mRNA Transcriptional Regulation; Lymphocyte Activation BATF basic leucine zipper transcription mRNA Transcriptional factor, ATF-like Regulation; Lymphocyte Activation; Cytokine Signaling ZEB1 zinc finger E-box binding mRNA Transcriptional homeobox 1 Regulation; Lymphocyte Activation; Cytokine Signaling TCF7 transcription factor 7 (T-cell mRNA Transcriptional specific, HMG-box) Regulation; Lymphocyte Activation; Host- pathogen Interaction RELB v-rel reticuloendotheliosis viral mRNA Transcriptional oncogene homolog B Regulation; NF-kB Signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling ETS1 v-ets erythroblastosis virus E26 mRNA Transcriptional oncogene homolog 1 (avian) Regulation; Oxidative Stress; Host- pathogen Interaction 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, mRNA Transcriptional cytoplasmic, calcineurin- Regulation; T Cell dependent 3 Receptor Signaling; Innate Immune System; Host- pathogen Interaction; B cell Receptor Signaling; Adaptive Immune System NFATC1 nuclear factor of activated T-cells, mRNA Transcriptional cytoplasmic, calcineurin- Regulation; T Cell dependent 1 Receptor Signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; B cell Receptor Signaling; Adaptive Immune System NFATC2 nuclear factor of activated T-cells, mRNA Transcriptional cytoplasmic, calcineurin- Regulation; T Cell dependent 2 Receptor Signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; B cell Receptor Signaling; Adaptive Immune System STAT4 signal transducer and activator of mRNA Transcriptional transcription 4 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 MAF v-maf musculoaponeurotic mRNA Transcriptional fibrosarcoma oncogene homolog Regulation; Th2 (avian) Differentiation STAT5A signal transducer and activator of mRNA Transcriptional transcription 5A 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 mRNA Transcriptional transcription 5B Regulation; Th2 Differentiation; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling; Chemokine Signaling STAT6 signal transducer and activator of mRNA Transcriptional transcription 6, interleukin-4 Regulation; Th2 induced Differentiation; Oxidative Stress; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling NFKB2 nuclear factor of kappa light mRNA Transcriptional polypeptide gene enhancer in B- Regulation; TLR cells 2 (p49/p100) Signaling; NLR signaling; NF-kB Signaling; Innate Immune System; Inflammasomes; Host-pathogen Interaction; Cytokine Signaling NFKBIA nuclear factor of

kappa light mRNA Transcriptional polypeptide gene enhancer in B- Regulation; TLR cells inhibitor, alpha Signaling; TNF Family Signaling; T Cell Receptor Signaling; NLR signaling; NF-kB 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 mRNA Transcriptional polypeptide gene enhancer in B- Regulation; TLR cells 1 Signaling; TNF Family Signaling; Th1 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 RELA v-rel reticuloendotheliosis viral mRNA Transcriptional oncogene homolog A (avian) 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 BCL3 B-cell CLL/lymphoma 3 mRNA Transcriptional Regulation; TNF Family Signaling; Lymphocyte Activation CEBPB CCAAT/enhancer binding protein mRNA Transcriptional (C/EBP), beta 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 mRNA Treg receptor 1 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 mRNA Treg receptor II (70/80 kDa) Differentiation; Th17 Differentiation; TGF-b Signaling; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling TGFB1 transforming growth factor, beta 1 mRNA Treg Differentiation; Th17 Differentiation; TGF-b 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 mRNA Treg transcription 3 (acute-phase Differentiation; response factor) 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 mRNA Type I Interferon tetratricopeptide repeats 2 Signaling; Cytokine Signaling IFITM1mcfarlin@ interferon induced transmembrane mRNA Type I Interferon unt.edu protein 1 Signaling; Cytokine (9-27) Signaling; B cell Receptor Signaling; Adaptive Immune System MX1 myxovirus (influenza virus) mRNA Type I Interferon resistance 1, interferon-inducible Signaling; Host- protein p78 (mouse) pathogen Interaction; Cytokine Signaling BST2 bone marrow stromal cell antigen mRNA Type I Interferon 2 Signaling; Lymphocyte Activation; Innate Immune System; Cytokine Signaling PSMB8 proteasome (prosome, macropain) mRNA Type I Interferon subunit, beta type, 8 (large Signaling; T Cell multifunctional peptidase 7) Receptor Signaling; NF-kB Signaling; MHC Class I Antigen Presentation; Innate Immune System; Immuno- metabolism; Cytokine Signaling; B cell Receptor Signaling; Apoptosis; Adaptive Immune System IFNA1/13 interferon, alpha 1/interferon, mRNA Type I Interferon alpha 13 Signaling; TLR Signaling; NLR signaling; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling IFNAR1 interferon (alpha, beta and omega) mRNA Type I Interferon receptor 1 Signaling; TLR Signaling; NLR signaling; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling IFNAR2 interferon (alpha, beta and omega) mRNA Type I Interferon receptor 2 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 mRNA Type I Interferon transcription 2, 113 kDa Signaling; Transcr iptional 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 mRNA Type II Interferon complex, transactivator Signaling; Host-pathogen Interaction; Cytokine Signaling PTAFR platelet-activating factor receptor mRNA Type II Interferon Signaling; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling CD44 CD44 molecule (Indian blood mRNA Type II Interferon group) 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, mRNA Type II Interferon interferon-inducible 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 mRNA Type II Interferon Ia, receptor (CD64)/Fc fragment of Signaling; Phagocytosis and IgG, high affinity Ib, receptor Degradation; MHC (CD64) Class I Antigen Presentation; Innate Immune System; Host-pathogen Interaction; Cytokine Signaling; Adaptive Immune System HLA-DPA1 major histocompatibility complex, mRNA Type II Interferon class II, DP alpha 1 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, mRNA Type II Interferon class II, DP beta 1 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-DQA1 major histocompatibility complex, mRNA Type II Interferon class II, DQ alpha 1 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, mRNA Type II Interferon class II, DQ beta 1 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, mRNA Type II Interferon class II, DR alpha 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, mRNA Type II Interferon class II, DR beta 1 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, mRNA Type II Interferon class II, DR beta 3 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 IFNGR1 interferon gamma receptor 1 mRNA Type II Interferon Signaling; Th1

Differentiation; Lymphocyte Activation; Host- pathogen Interaction; Cytokine Signaling IFNG interferon, gamma mRNA Type II Interferon Signaling; Th1 Differentiation; TGF-b 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-kB 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-kB Signaling; Lymphocyte Trafficking; Lymphocyte Activation; Host-pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System HLA-A major histocompatibility complex, mRNA Type II Interferon class I, A 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, mRNA Type II Interferon class I, B Signaling; Type I Interferon Signaling; Phagocytosis and Degradation; MHC Class I Antigen Presentation; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Cytokine Signaling; Cell Adhesion; Adaptive Immune System HLA-C major histocompatibility complex, mRNA Type II Interferon class I, C Signaling; Type I Interferon Signaling; 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- mRNA Type II Interferon receptor type 6 Signaling; Type I Interferon Signaling; T Cell Receptor Signaling; Lymphocyte Activation; Innate Immune System; Host- pathogen Interaction; Hemostasis; Cytokine Signaling; B cell Receptor Signaling; Adaptive Immune System SOCS1 suppressor of cytokine signaling 1 mRNA Type II Interferon Signaling; Type I Interferon Signaling; TLR Signaling; 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 Signaling; Type I Interferon Signaling; TNF Family Signaling; MHC Class I Antigen Presentation; Host- pathogen Interaction; Cytokine Signaling; Adaptive Immune System IRF8 interferon regulatory factor 8 mRNA Type II Interferon Signaling; Type I Interferon Signaling; Transcriptional Regulation; Host- pathogen Interaction; Cytokine Signaling 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 mRNA Type II Interferon transcription 1, 91 kDa 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 Differentiation; NLR signaling; Host- pathogen Interaction; Hemostasis; Cytokine Signaling

Claims

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.
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.