(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 December 2018 (20.12.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/232288 A1

(51) International Patent Classification:
A61K 31/5377 (2006.01) *G01N 33/564* (2006.01)

(21) International Application Number:
PCT/US2018/037826

(22) International Filing Date:
15 June 2018 (15.06.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/521,299 16 June 2017 (16.06.2017) US

(71) Applicant *(for all designated States except AL, AT, BA, BE, BG, CH, CN, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IN, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR)*: **GENENTECH, INC.** [US/US]; 1 Dna Way, South San Francisco, CA 94080-4990 (US).

(71) Applicant *(for AL, AT, BA, BE, BG, CH, CN, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IN, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR only)*: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, 4070 Basel (CH).

(72) Inventors: **HACKNEY, Jason**; 1 Dna Way, South San Francisco, CA 94080-4990 (US). **SETIADI, Alvernia, Francesca**; 1 Dna Way, South San Francisco, CA 94080-4990 (US). **TOWNSEND, Michael**; 1 Dna Way, South San Francisco, CA 94080-4990 (US). **ZARRIN, Ali, A.**; 1 Dna Way, South San Francisco, CA 94080-4990 (US).

(74) Agent: **ELBING, Karen, L.**; Calrk & Elbing LLP, 101 Federal Street, 15th Floor, Boston, MA 02110 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*

WO 2018/232288 A1

(54) Title: DIAGNOSTIC AND THERAPEUTIC METHODS FOR IRAK4-MEDIATED DISORDERS AND CONDITIONS

(57) Abstract: The present invention provides diagnostic and therapeutic methods and compositions for treating a patient suffering from an interleukin-1 receptor-associated kinase 4 (IRAK4)-mediated disorder or condition, such as an immune disorder (e.g., systemic lupus erythematosus (SLE)) or an inflammatory disorder (e.g., asthma). The invention provides diagnostic methods of monitoring the response of a patient having an IRAK4-mediated disorder or condition to treatment including an IRAK4 pathway inhibitor, methods of identifying a patient having an IRAK4-mediated disorder or condition who may benefit from treatment including an IRAK4 pathway inhibitor, and methods of selecting a therapy for a patient having an IRAK4-mediated disorder or condition based on the expression level of one or more IRAK4 biomarkers (e.g., one or more genes set forth in Table 1). Related therapeutic methods and compositions (e.g., diagnostic kits) are also provided.

DIAGNOSTIC AND THERAPEUTIC METHODS FOR IRAK4-MEDIATED DISORDERS AND CONDITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit to U.S. Provisional Application No. 62/521,299, filed on June 16, 2017, which is incorporated by reference herein in its entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 14, 2018, is named 50474-170WO2_Sequence_Listing_6.14.18_ST25 and is 142,784 bytes in size.

FIELD OF THE INVENTION

The present invention is directed to diagnostic and therapeutic methods for the treatment of interleukin-1 receptor-associated kinase 4 (IRAK4)-mediated disorders or conditions (e.g., immune disorders (e.g., systemic lupus erythematosus (SLE)) or inflammatory disorders (e.g., asthma)) using IRAK4 pathway inhibitors (e.g., an IRAK4 small molecule inhibitor). Also provided are related compositions (e.g., diagnostic kits).

BACKGROUND

The interleukin-1 receptor-associated kinase (IRAK) family is comprised of four family members IRAK1, IRAK2, IRAK3 (also termed IRAK-M), and IRAK4. These proteins are characterized by a typical N-terminal death domain that mediates interaction with MyD88-family adaptor proteins and a centrally located kinase domain. Whereas IRAK1 and IRAK4 have kinase activity, IRAK2 and IRAK3 are catalytically inactive. Upon activation of their upstream cognate receptors, IRAK4 is thought to phosphorylate IRAK1, resulting in the activation and auto-phosphorylation of IRAK1 and subsequent phosphorylation of downstream substrates. The hyper-phosphorylation of IRAK1 directs its dissociation from the receptor complex and its eventual ubiquitylation and proteasomal degradation. Phosphorylation of downstream substrates such as Pellino-2 ultimately leads to the activation of the MAPKs, such as p38, c-Jun N-terminal kinase (JNK), and NF-kB, followed by production of pro-inflammatory cytokines, chemokines, and destructive enzymes.

The role of IRAK4, in particular, in innate immunity and pathogenesis of autoimmune and inflammatory disorders is emerging. See, e.g., Li et al. *PNAS.* 99(8): 5567-5572, 2002 and Flannery et al. *Biochem. Pharm.* 80(12): 1981-1991, 2010. Patients with destabilizing or null mutations in IRAK4 demonstrate defects in toll-like receptor (TLR) signaling and the production of pro-inflammatory cytokines, such as IL-1 and TNF, as well as antiviral cytokines, such as IFNα and IFNβ. These patients demonstrate an increased susceptibility to gram-positive bacterial infections, although they are generally resistant to gram-negative bacterial, viral, and fungal infections. Similarly, IRAK4-deficient mice have defects in TLR- and IL-1-mediated cytokine production and exhibit an increased susceptibility to infection. Not surprisingly, the IRAK4 pathway has been suggested to be involved in various disorders and

conditions, including inflammatory, immune-related, and cell proliferative disorders and conditions associated with IRAK-mediated signal transduction, for which there remains an unmet need to develop improved diagnostic methods for identifying patient populations best suited for treatment including an IRAK4 pathway inhibitor (e.g., an IRAK4 small molecule inhibitor).

SUMMARY OF THE INVENTION

The present invention provides diagnostic methods, therapeutic methods, and kits for the treatment of IRAK4-mediated disorders or conditions (e.g., immune disorders and inflammatory disorders).

In a first aspect, the invention features a method of monitoring the response of a patient having an interleukin-1 receptor-associated kinase 4 (IRAK4)-mediated disorder or condition to treatment comprising an IRAK4 pathway inhibitor, the method comprising: (a) determining, in a sample obtained from the patient at a time point following administration of a first dose of the IRAK4 pathway inhibitor, the expression level of one or more genes set forth in Table 1 (i.e., CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, BCL2A1, CXCL10, CCL8, GPR84, C15orf48, DRAM1, CXCL11, TNFAIP6, CSRNP1, PLSCR1, CLEC4E, SAMSN1, and ACSL1), and (b) comparing the expression level of the one or more genes set forth in Table 1 in the sample with a reference expression level, thereby monitoring the response of the patient to treatment comprising the IRAK4 pathway inhibitor. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1. In some embodiments, the one or more genes set forth in Table 1 comprises all nine of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1. In some embodiments, the one or more genes set forth in Table 1 comprises all 11 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3. In some embodiments, the one or more genes set forth in Table 1 comprises all 12 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1. In some embodiments, the one or more genes set forth in Table 1 are all 24 genes set forth in Table 1.

In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased in the sample obtained from the patient relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased at least about 0.5-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased at least about 1-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased at least about 2-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased at least about 3-fold relative

to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased at least about 4-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased at least about 5-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased at least about 10-fold relative to the reference expression level. In some embodiments, the decreased expression level of the one or more genes set forth in Table 1 indicates that the patient is responding to the IRAK4 pathway inhibitor. In some embodiments, the method further comprises administering at least a second dose of an IRAK4 pathway inhibitor to a patient whose expression level of the one or more genes set forth in Table 1 is decreased relative to the reference expression level.

In a second aspect, the invention features a method of treating a patient having an IRAK4-mediated disorder or condition with an IRAK4 pathway inhibitor, the method comprising: (a) determining, in a sample obtained from the patient at a time point following administration of a first dose of the IRAK4 pathway inhibitor, the expression level of one or more genes set forth in Table 1 (i.e., CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, BCL2A1, CXCL10, CCL8, GPR84, C15orf48, DRAM1, CXCL11, TNFAIP6, CSRNP1, PLSCR1, CLEC4E, SAMSN1, and ACSL1), (b) comparing the expression level of the one or more genes set forth in Table 1 in the sample with a reference expression level, and (c) administering at least a second dose of the IRAK4 pathway inhibitor to the patient based on a decreased expression level of the one or more genes set forth in Table 1 relative to the reference expression level. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1. In some embodiments, the one or more genes set forth in Table 1 comprises all nine of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1. In some embodiments, the one or more genes set forth in Table 1 comprises all 11 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3. In some embodiments, the one or more genes set forth in Table 1 comprises all 12 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1. In some embodiments, the one or more genes set forth in Table 1 are all 24 genes set forth in Table 1. In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased at least about 0.5-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased at least about 1-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased at least about 2-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased at least about 3-fold relative to the reference expression level. In some embodiments, the expression level of the

one or more genes set forth in Table 1 is decreased at least about 4-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased at least about 5-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is decreased at least about 10-fold relative to the reference expression level.

In some embodiments of any of the preceding aspects, the reference expression level is: (i) the expression level of the one or more genes set forth in Table 1 in a sample from the patient obtained prior to administration of the first dose of the IRAK4 pathway inhibitor; (ii) the expression level of the one or more genes set forth in Table 1 in a reference population; (iii) a pre-assigned expression level for the one or more genes set forth in Table 1; (iv) the expression level of the one or more genes set forth in Table 1 in a sample obtained from the patient at a previous time point, wherein the previous time point is following administration of the first dose of the IRAK4 pathway inhibitor; or (v) the expression level of the one or more genes set forth in Table 1 in a sample obtained from the patient at a subsequent time point.

In a third aspect, the invention features method of identifying a patient having an IRAK4-mediated disorder or condition who may benefit from treatment comprising an IRAK4 pathway inhibitor, the method comprising determining an expression level of one or more genes set forth in Table 1 (i.e., CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, BCL2A1, CXCL10, CCL8, GPR84, C15orf48, DRAM1, CXCL11, TNFAIP6, CSRNP1, PLSCR1, CLEC4E, SAMSN1, and ACSL1) in a sample obtained from the patient, wherein an increased expression level of the one or more genes set forth in Table 1 in the sample as compared to a reference expression level identifies the patient as one who may benefit from treatment comprising an IRAK4 pathway inhibitor.

In a fourth aspect, the invention features a method of selecting a therapy for a patient having an IRAK4-mediated disorder or condition, the method comprising determining an expression level of one or more genes set forth in Table 1 (i.e., CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, BCL2A1, CXCL10, CCL8, GPR84, C15orf48, DRAM1, CXCL11, TNFAIP6, CSRNP1, PLSCR1, CLEC4E, SAMSN1, and ACSL1) in a sample obtained from the patient, wherein an increased expression level of the one or more genes set forth in Table 1 in the sample as compared to a reference expression level identifies the patient as one who may benefit from treatment comprising an IRAK4 pathway inhibitor.

In some embodiments of the third or fourth aspect, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1. In some embodiments, the one or more genes set forth in Table 1 comprises all nine of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1. In some embodiments, the one or more genes set forth in Table 1 comprises all 11 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and

PFKFB3. In some embodiments, the one or more genes set forth in Table 1 comprises all 12 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1. In some embodiments, the one or more genes set forth in Table 1 are all 24 genes set forth in Table 1. In some embodiments, the expression level of the one or more genes set forth in Table 1 is increased in the sample obtained from the patient relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is increased at least about 0.5-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is increased at least about 1-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is increased at least about 2-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is increased at least about 3-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is increased at least about 4-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is increased at least about 5-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 is increased at least about 10-fold relative to the reference expression level. In some embodiments, the patient has an increased expression level of the one or more genes set forth in Table 1 relative to the reference expression level and the method further comprises administering to the patient an IRAK4 pathway inhibitor.

In fifth aspect, the invention features a method of treating a patient having an IRAK4-mediated disorder or condition, the method comprising administering to the patient an IRAK4 pathway inhibitor, wherein prior to treatment the expression level of one or more genes set forth in Table 1 (i.e., CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, BCL2A1, CXCL10, CCL8, GPR84, C15orf48, DRAM1, CXCL11, TNFAIP6, CSRNP1, PLSCR1, CLEC4E, SAMSN1, and ACSL1) in a sample obtained from the patient has been determined to be increased relative to a reference expression level. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1. In some embodiments, the one or more genes set forth in Table 1 comprises all nine of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1. In some embodiments, the one or more genes set forth in Table 1 comprises all 11 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3. In some embodiments, the one or more genes set forth in Table 1 comprises all 12 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1. In some embodiments, the one or more genes set forth in Table 1 are all 24 genes set forth in Table 1. In some embodiments, the expression level of the one or more genes set forth in Table 1 have

been determined to be increased at least about 0.5-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 have been determined to be increased at least about 1-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 have been determined to be increased at least about 2-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 have been determined to be increased at least about 3-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 have been determined to be increased at least about 4-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 have been determined to be increased at least about 5-fold relative to the reference expression level. In some embodiments, the expression level of the one or more genes set forth in Table 1 have been determined to be increased at least about 10-fold relative to the reference expression level.

In some embodiments of any one of the third, fourth, and fifth aspects, the reference expression level is: (i) the expression level of the one or more genes set forth in Table 1 in a reference population; or (ii) a pre-assigned expression level for the one or more genes set forth in Table 1.

In some embodiments of any one of the preceding aspects, the expression level of the one or more genes set forth in Table 1 in a reference population is a median expression level of the one or more genes set forth in Table 1 in a reference population.

In some embodiments of any one of the preceding aspects, the sample obtained from the patient is a tissue sample, a whole blood sample, a plasma sample, or a serum sample. In some embodiments, the sample obtained from the patient is a blood sample (e.g., a whole blood sample).

In some embodiments of any one of the preceding aspects, the expression level is an mRNA expression level. In some embodiments, the mRNA expression level is determined by RNA-Seq, qPCR, microarray analysis, gene expression profiling, serial analysis of gene expression, or whole genome sequencing. In some embodiments, the mRNA expression level is determined by qPCR. In other embodiments of any one of the preceding aspects, the expression level is a protein expression level.

In some embodiments of any one of the preceding aspects, the IRAK4-mediated disorder or condition is selected from the group consisting of an immune disorder, an inflammatory disorder, a fibrotic disorder, an eosinophilic disorder, an infection, pain, a central nervous system disorder, an acute kidney injury, a chronic kidney disease, endometriosis, non-alcoholic fatty liver disease, a metabolic syndrome, and obesity. In some embodiments, the immune disorder is lupus, asthma, atopic dermatitis, rheumatoid arthritis, inflammatory bowel disease (IBD), Crohn's disease, or ulcerative colitis. In some embodiments, the inflammatory disorder is lupus, asthma, atopic dermatitis, rheumatoid arthritis, inflammatory bowel disease (IBD), Crohn's disease, or ulcerative colitis. In some embodiments, the lupus is systemic lupus erythematosus (SLE). In some embodiments, the lupus is lupus nephritis.

In some embodiments of any one of the preceding aspects, the IRAK4 pathway inhibitor is an IRAK4 inhibitor, an IRAK1 inhibitor, a toll-like receptor (TLR) inhibitor, an interleukin-1 receptor (IL-1R) inhibitor, an interleukin-33 receptor (IL-33R) inhibitor, or a myeloid differentiation primary response gene 88 (MyD88) inhibitor. In some embodiments, the IRAK4 pathway inhibitor is an IRAK4 inhibitor. In some

embodiments, the IRAK4 pathway inhibitor is a TLR inhibitor. In some embodiments, the TLR inhibitor is a TLR7 inhibitor, a TLR8 inhibitor, a TLR9 inhibitor, a TLR1 inhibitor, a TLR2 inhibitor, a TLR4 inhibitor, a TLR5 inhibitor, a TLR6 inhibitor, or a TLR10 inhibitor. In some embodiments, the TLR inhibitor is a TLR7 inhibitor, a TLR8 inhibitor, or both a TLR7 and TLR8 inhibitor. In some embodiments, the TLR inhibitor is a TLR9 inhibitor. In some embodiments, the IRAK4 pathway inhibitor is a small molecule inhibitor.

In some embodiments of any one of the preceding aspects, the method further comprises administering to the patient an additional therapeutic agent. In some embodiments, the additional therapeutic agent is a corticosteroid, a nonsteroidal anti-inflammatory drug (NSAID), chloroquine, hydroxychloroquine (PLAQUENIL®), cyclosporine, azathioprine, methotrexate, mycophenolate mofetil (CELLCEPT®), or cyclophosphamide (CYTOXAN®). In some embodiments, the IRAK4 pathway inhibitor and the additional therapeutic agent are co-administered. In some embodiments, the IRAK4 pathway inhibitor and the additional therapeutic agent are sequentially administered.

In another aspect, the invention features a kit for identifying a patient having an IRAK4-mediated disorder or condition who may benefit from treatment comprising an IRAK4 pathway inhibitor, the kit comprising: (a) polypeptides or polynucleotides capable of determining the expression level of one or more genes set forth in Table 1 (i.e., CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, BCL2A1, CXCL10, CCL8, GPR84, C15orf48, DRAM1, CXCL11, TNFAIP6, CSRNP1, PLSCR1, CLEC4E, SAMSN1, and ACSL1); and (b) instructions for using the polypeptides or polynucleotides to identify a patient having an IRAK4-mediated disorder or condition who may benefit from treatment comprising the IRAK4 pathway inhibitor. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3. In some embodiments, the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1. In some embodiments, the one or more genes set forth in Table 1 comprises all nine of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1. In some embodiments, the one or more genes set forth in Table 1 comprises all 11 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3. In some embodiments, the one or more genes set forth in Table 1 comprises all 12 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1. In some embodiments, the one or more genes set forth in Table 1 are all 24 genes set forth in Table 1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A is a heatmap showing that 285 genes from a microarray dataset of GEO Accession GSE25742 (Alsina et al. *Nat. Immunol.* 15:1134-42, 2014) showed significantly lower induction by the TLR7/8 stimulator R848 (resiquimod) in the whole blood from IRAK4-deficient patients compared to healthy patient controls (false discovery rate (FDR) < 0.05; fold-change (FC) > 1.25).

FIG. 1B is a graph showing the relative signature scores for the 285 genes that displayed significantly lower induction by R848 (resiquimod) in both IRAK4$^{-/-}$ and MyD88$^{-/-}$ patients as compared to R848-treated healthy patient controls.

FIG. 2 is a heatmap showing that IRAK4$^{-/-}$ patients failed to upregulate type I IFNs and other TLR-regulated genes in response to R848 compared to healthy patients.

FIG. 3 is a series of graphs showing three genes (IL1RN, CLEC4E, and SMSN1) out of 44 identified genes that are differentially upregulated in systemic lupus erythematosus (SLE) patients from two extra-renal cohorts (University of Michigan Cohort and ROSE Phase II Study Cohort) compared to healthy patients from the respective cohorts. $p < 0.05$; $FC > 1.2$.

FIG. 4 is a series of graphs showing that IRAK4 pathway biomarker genes (CXCL10 and CD38 shown) displayed significantly impaired induction by R848 in bone marrow-derived macrophages (BMDMs) from IRAK4 kinase-dead (KD) mice compared to IRAK4 wild-type mice.

FIG. 5 is a graph showing that IFNβ1 was induced by R848 to a significantly lower extend ($p = 0.02$) in IRAK4 KD mice compared to IRAK4 wild-type mice macrophages.

FIG. 6 is a table showing all 24 identified IRAK4 pathway biomarker genes and their respective expression levels following induction by R848 in human IRAK4$^{-/-}$ whole blood (left column) and IRAK4 KD mice macrophages (middle column) compared to healthy and wild-type controls, respectively. The right column shows the relative expression levels for each IRAK4 biomarker in SLE patients relative to healthy patient controls.

FIG. 7A is a graph showing that the expression level of the IFN-regulated gene OAS1A trends towards decreased induction by R848 in IRAK4 KD mice compared to IRAK4 wild-type mice ($p < 0.15$).

FIG. 7B is a graph showing that the expression level of the IFN-regulated gene OAS2 trends towards decreased induction by R848 in IRAK4 KD mice compared to IRAK4 wild-type mice ($p < 0.15$).

FIG. 7C is a graph showing that the expression level of the IFN-regulated gene IFIT1 trends towards decreased induction by R848 in IRAK4 KD mice compared to IRAK4 wild-type mice ($p < 0.15$).

FIG. 7D is a graph showing that the expression level of the IFN-regulated gene IFNA5 trends towards decreased induction by R848 in IRAK4 KD mice compared to IRAK4 wild-type mice ($p < 0.15$).

FIG. 7E is a graph showing that the expression level of the IFN-regulated gene MX1 trends towards decreased induction by R848 in IRAK4 KD mice compared to IRAK4 wild-type mice ($p < 0.15$).

FIG. 8 is a table showing the results of dose-escalation experiments using two distinct IRAK4 small molecule inhibitors G03074387 (G-4387) (BMS) and G03081557 (G-1557) (Pfizer) in human whole blood samples, with or without stimulation by R848. IRAK4 biomarker genes that displayed a dose-dependent downregulation by the test IRAK4 small molecule inhibitor in at least two out of three of the tested human donor samples is identified by a "Y."

FIG. 9 is a series of graphs showing the percent decrease in expression of the top nine IRAK4 biomarker genes, which displayed dose-dependent downregulation by both IRAK4 small molecule inhibitors G-4387 and G-1557. Respective p-values are also shown.

FIG. 10A is a heatmap showing the correlation coefficients for the denoted 12 IRAK4 biomarker genes, as determined from SLE patient blood samples (whole blood samples) from the ROSE Phase II Study Cohort described herein.

FIG. 10B is a heatmap showing the correlation coefficients for the denoted 12 IRAK4 biomarker genes, as determined from SLE patient blood samples (PBMC samples) from the University of Michigan Cohort described herein.

DETAILED DESCRIPTION OF THE INVENTION

I. Introduction

The present invention provides diagnostic methods, therapeutic methods, and compositions for the treatment of interleukin-1 receptor-associated kinase 4 (IRAK4)-mediated disorders or conditions (e.g., immune disorders (e.g., systemic lupus erythematosus) or inflammatory disorders (e.g., asthma). The invention is based, at least in part, on the discovery that expression levels of particular IRAK4 pathway genes (e.g., CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, BCL2A1, CXCL10, CCL8, GPR84, C15orf48, DRAM1, CXCL11, TNFAIP6, CSRNP1, PLSCR1, CLEC4E, SAMSN1, and ACSL1) can be used as biomarkers (e.g., prognostic biomarkers and/or predictive biomarkers) in diagnostic methods of monitoring the response of a patient having an IRAK4-mediated disorder or condition to treatment including an IRAK4 pathway inhibitor, methods of identifying a patient having an IRAK4-mediated disorder who may benefit from treatment including an IRAK4 pathway inhibitor, and methods of selecting a therapy for a patient having an IRAK4-mediated disorder or condition based on the expression level of one or more IRAK4 pathway genes. Also provided are related therapeutic methods and diagnostic kits.

II. Definitions

It is to be understood that aspects and embodiments of the invention described herein include "comprising," "consisting," and "consisting essentially of" aspects and embodiments. As used herein, the singular form "a," "an," and "the" includes plural references unless indicated otherwise.

The term "about" as used herein refers to the usual error range for the respective value readily known to the skilled person in this technical field. Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter *per se*. For example, description referring to "about X" includes description of "X."

The term "IRAK4 pathway inhibitor" refers to a molecule that decreases, blocks, inhibits, abrogates, or interferes with signal transduction through a pathway within which IRAK4 functions. In some embodiments, an IRAK4 pathway inhibitor may inhibit the activity of one or more proteins involved in the activation of IRAK4 signaling. In some embodiments, an IRAK4 signaling inhibitor may activate the activity of one or more proteins involved in the inhibition of IRAK4 signaling. IRAK4 pathway inhibitors include, but are not limited to, an IRAK4 inhibitor, an IRAK1 inhibitor, a toll-like receptor (TLR) inhibitor, an interleukin-1 receptor (IL-1R) inhibitor, an interleukin-33 receptor (IL-33R) inhibitor, or a myeloid differentiation primary response gene 88 (MyD88) inhibitor.

The term "IRAK4 inhibitor" or "IRAK4 antagonist" refers to molecule that decreases, blocks, inhibits, abrogates, or interferes with IRAK4 activation or function. In a particular embodiment, an IRAK4 inhibitor has a binding affinity (dissociation constant) to IRAK4 of about 1,000 nM or less. In another

embodiment, an IRAK4 inhibitor has a binding affinity to IRAK4 of about 100 nM or less. In another embodiment, an IRAK4 inhibitor has a binding affinity to IRAK4 of about 50 nM or less. In another embodiment, an IRAK4 inhibitor has a binding affinity to IRAK4 of about 10 nM or less. In another embodiment, an IRAK4 inhibitor has a binding affinity to IRAK4 of about 1 nM or less. In a particular embodiment, an IRAK4 inhibitor inhibits IRAK4 signaling with an IC50 of 1,000 nM or less. In another embodiment, an IRAK4 inhibitor inhibits IRAK4 signaling with an IC50 of 500 nM or less. In another embodiment, an IRAK4 inhibitor inhibits IRAK4 signaling with an IC50 of 50 nM or less. In another embodiment, an IRAK4 inhibitor inhibits IRAK4 signaling with an IC50 of 10 nM or less. In another embodiment, an IRAK4 inhibitor inhibits IRAK4 signaling with an IC50 of 1 nM or less. In some embodiments, the IRAK4 inhibitor is a small molecule inhibitor of IRAK4.

The term “IRAK1 inhibitor” or “IRAK1 antagonist” refers to molecule that decreases, blocks, inhibits, abrogates, or interferes with IRAK1 activation or function. In a particular embodiment, an IRAK1 inhibitor has a binding affinity (dissociation constant) to IRAK1 of about 1,000 nM or less. In another embodiment, an IRAK1 inhibitor has a binding affinity to IRAK1 of about 100 nM or less. In another embodiment, an IRAK1 inhibitor has a binding affinity to IRAK1 of about 50 nM or less. In another embodiment, an IRAK1 inhibitor has a binding affinity to IRAK1 of about 10 nM or less. In another embodiment, an IRAK1 inhibitor has a binding affinity to IRAK1 of about 1 nM or less. In a particular embodiment, an IRAK1 inhibitor inhibits IRAK1 signaling with an IC50 of 1,000 nM or less. In another embodiment, an IRAK1 inhibitor inhibits IRAK1 signaling with an IC50 of 500 nM or less. In another embodiment, an IRAK1 inhibitor inhibits IRAK1 signaling with an IC50 of 50 nM or less. In another embodiment, an IRAK1 inhibitor inhibits IRAK1 signaling with an IC50 of 10 nM or less. In another embodiment, an IRAK1 inhibitor inhibits IRAK1 signaling with an IC50 of 1 nM or less. In some embodiments, the IRAK1 inhibitor is a small molecule inhibitor of IRAK1.

The term “toll-like receptor inhibitor,” “toll-like receptor antagonist,” “TLR inhibitor,” or “TLR antagonist” refers to molecule that decreases, blocks, inhibits, abrogates, or interferes with TLR (e.g., TLR7, TLR8, TLR9, TLR1, TLR2, TLR4, TLR5, TLR6, and/or TLR10) activation or function. In a particular embodiment, a TLR inhibitor has a binding affinity (dissociation constant) to TLR of about 1,000 nM or less. In another embodiment, a TLR inhibitor has a binding affinity to TLR of about 100 nM or less. In another embodiment, a TLR inhibitor has a binding affinity to TLR of about 50 nM or less. In another embodiment, a TLR inhibitor has a binding affinity to TLR of about 10 nM or less. In another embodiment, a TLR inhibitor has a binding affinity to TLR of about 1 nM or less. In a particular embodiment, a TLR inhibitor inhibits TLR signaling with an IC50 of 1,000 nM or less. In another embodiment, a TLR inhibitor inhibits TLR signaling with an IC50 of 500 nM or less. In another embodiment, a TLR inhibitor inhibits TLR signaling with an IC50 of 50 nM or less. In another embodiment, a TLR inhibitor inhibits TLR signaling with an IC50 of 10 nM or less. In another embodiment, a TLR inhibitor inhibits TLR signaling with an IC50 of 1 nM or less. In some embodiments, the TLR inhibitor is a small molecule inhibitor of one or more TLRs.

The term “interleukin-1 receptor inhibitor,” “interleukin-1 receptor antagonist,” “IL-1R inhibitor,” or “IL-1R antagonist” refers to molecule that decreases, blocks, inhibits, abrogates, or interferes with IL-1R activation or function. In a particular embodiment, an IL-1R inhibitor has a binding affinity (dissociation

constant) to IL-1R of about 1,000 nM or less. In another embodiment, an IL-1R inhibitor has a binding affinity to IL-1R of about 100 nM or less. In another embodiment, an IL-1R inhibitor has a binding affinity to IL-1R of about 50 nM or less. In another embodiment, an IL-1R inhibitor has a binding affinity to IL-1R of about 10 nM or less. In another embodiment, an IL-1R inhibitor has a binding affinity to IL-1R of about 1 nM or less. In a particular embodiment, an IL-1R inhibitor inhibits IL-1R signaling with an IC50 of 1,000 nM or less. In another embodiment, an IL-1R inhibitor inhibits IL-1R signaling with an IC50 of 500 nM or less. In another embodiment, an IL-1R inhibitor inhibits IL-1R signaling with an IC50 of 50 nM or less. In another embodiment, an IL-1R inhibitor inhibits IL-1R signaling with an IC50 of 10 nM or less. In another embodiment, an IL-1R inhibitor inhibits IL-1R signaling with an IC50 of 1 nM or less. In some embodiments, the IL-1R inhibitor is a small molecule inhibitor of IL-1R.

The term “interleukin-33 receptor inhibitor,” “interleukin-33 receptor antagonist,” “IL-33R inhibitor,” or “IL-33R antagonist” refers to molecule that decreases, blocks, inhibits, abrogates, or interferes with IL-33R activation or function. In a particular embodiment, an IL-33R inhibitor has a binding affinity (dissociation constant) to IL-33R of about 1,000 nM or less. In another embodiment, an IL-33R inhibitor has a binding affinity to IL-33R of about 100 nM or less. In another embodiment, an IL-33R inhibitor has a binding affinity to IL-33R of about 50 nM or less. In another embodiment, an IL-33R inhibitor has a binding affinity to IL-33R of about 10 nM or less. In another embodiment, an IL-33R inhibitor has a binding affinity to IL-33R of about 1 nM or less. In a particular embodiment, an IL-33R inhibitor inhibits IL-33R signaling with an IC50 of 1,000 nM or less. In another embodiment, an IL-33R inhibitor inhibits IL-33R signaling with an IC50 of 500 nM or less. In another embodiment, an IL-33R inhibitor inhibits IL-33R signaling with an IC50 of 50 nM or less. In another embodiment, an IL-33R inhibitor inhibits IL-33R signaling with an IC50 of 10 nM or less. In another embodiment, an IL-33R inhibitor inhibits IL-33R signaling with an IC50 of 1 nM or less. In some embodiments, the IL-33R inhibitor is a small molecule inhibitor of IL-33R.

The term “myeloid differentiation primary response gene 88 inhibitor,” “myeloid differentiation primary response gene 88 antagonist,” “MyD88 inhibitor,” or “MyD88 antagonist” refers to molecule that decreases, blocks, inhibits, abrogates, or interferes with MyD88 activation or function. In a particular embodiment, a MyD88 inhibitor has a binding affinity (dissociation constant) to MyD88 of about 1,000 nM or less. In another embodiment, a MyD88 inhibitor has a binding affinity to MyD88 of about 100 nM or less. In another embodiment, a MyD88 inhibitor has a binding affinity to MyD88 of about 50 nM or less. In another embodiment, a MyD88 inhibitor has a binding affinity to MyD88 of about 10 nM or less. In another embodiment, a MyD88 inhibitor has a binding affinity to MyD88 of about 1 nM or less. In a particular embodiment, a MyD88 inhibitor inhibits MyD88 signaling with an IC50 of 1,000 nM or less. In another embodiment, a MyD88 inhibitor inhibits MyD88 signaling with an IC50 of 500 nM or less. In another embodiment, a MyD88 inhibitor inhibits MyD88 signaling with an IC50 of 50 nM or less. In another embodiment, a MyD88 inhibitor inhibits MyD88 signaling with an IC50 of 10 nM or less. In another embodiment, a MyD88 inhibitor inhibits MyD88 signaling with an IC50 of 1 nM or less. In some embodiments, the MyD88 inhibitor is a small molecule inhibitor of MyD88.

The term “CD38” refers to cluster of differentiation 38 and encompasses homologues, mutations, and isoforms thereof. CD38 is also referred to in the art as ADPRC1. The term encompasses full-length,

unprocessed CD38, as well as any form of CD38 that results from processing in the cell. The term encompasses naturally occurring variants of CD38 (e.g., splice variants or allelic variants). The term encompasses, for example, the CD38 gene, the mRNA sequence of human CD38 (e.g., SEQ ID NO: 1; GenBank Accession No. NM_001775.3), and the amino acid sequence of human CD38 (e.g., SEQ ID NO: 2; UniProtKB Accession No. P28907) as well as CD38 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "SOCS3" refers to Suppressor Of Cytokine Signaling 3 and encompasses homologues, mutations, and isoforms thereof. SOCS3 is also referred to in the art as Cytokine-Inducible SH2 Protein 3 (CIS3), STAT-Induced STAT Inhibitor 3 (SSI3), and ATOD4. The term encompasses full-length, unprocessed SOCS3, as well as any form of SOCS3 that results from processing in the cell. The term encompasses naturally occurring variants of SOCS3 (e.g., splice variants or allelic variants). The term encompasses, for example, the SOCS3 gene, the mRNA sequence of human SOCS3 (e.g., SEQ ID NO: 3; GenBank Accession No. NM_003955.4), and the amino acid sequence of human SOCS3 (e.g., SEQ ID NO: 4; UniProtKB Accession No. O14543) as well as SOCS3 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "AQP9" refers to aquaporin 9 and encompasses homologues, mutations, and isoforms thereof. AQP9 is also referred to in the art as Aquaglyceroporin-9, HsT17287, T17287, and Small Solute Channel 1 (SSC1). The term encompasses full-length, unprocessed AQP9, as well as any form of AQP9 that results from processing in the cell. The term encompasses naturally occurring variants of AQP9 (e.g., splice variants or allelic variants). The term encompasses, for example, the AQP9 gene, the mRNA sequence of human AQP9 (e.g., SEQ ID NO: 5; GenBank Accession No. NM_020980.4), and the amino acid sequence of human AQP9 (e.g., SEQ ID NO: 6; UniProtKB Accession No. O43315) as well as AQP9 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "CDKN1A" refers to Cyclin Dependent Kinase Inhibitor 1A and encompasses homologues, mutations, and isoforms thereof. CDKN1A is also referred to in the art as CDK-Interacting Protein 1 (CIP1), Melanoma Differentiation Associated Protein 6 (MDA-6), or Wild-Type P53-Activated Fragment 1 (WAF-1). The term encompasses full-length, unprocessed CDKN1A, as well as any form of CDKN1A that results from processing in the cell. The term encompasses naturally occurring variants of CDKN1A (e.g., splice variants or allelic variants). The term encompasses, for example, the CDKN1A gene, the mRNA sequence of human CDKN1A (e.g., SEQ ID NO: 7; GenBank Accession No. NM_000389), and the amino acid sequence of human CDKN1A (e.g., SEQ ID NO: 8; UniProtKB Accession No. P38936) as well as CDKN1A DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "GADD45B" refers to Growth Arrest And DNA Damage Inducible Beta and encompasses homologues, mutations, and isoforms thereof. GADD45B is also referred to in the art as Myeloid Differentiation Primary Response Protein MyD118 (MYD118). The term encompasses full-length, unprocessed GADD45B, as well as any form of GADD45B that results from processing in the cell. The term encompasses naturally occurring variants of GADD45B (e.g., splice variants or allelic variants). The term encompasses, for example, the GADD45B gene, the mRNA sequence of human GADD45B

(e.g., SEQ ID NO: 9; GenBank Accession No. NM_015675), and the amino acid sequence of human GADD45B (e.g., SEQ ID NO: 10; UniProtKB Accession No. O75293) as well as GADD45B DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "B4GALT5" refers to Beta-1,4-Galactosyltransferase 5 and encompasses homologues, mutations, and isoforms thereof. B4GALT5 is also referred to in the art as UDP-Galactose: Beta-N-Acetylglucosamine. The term encompasses full-length, unprocessed B4GALT5, as well as any form of B4GALT5 that results from processing in the cell. The term encompasses naturally occurring variants of B4GALT5 (e.g., splice variants or allelic variants). The term encompasses, for example, the B4GALT5 gene, the mRNA sequence of human B4GALT5 (e.g., SEQ ID NO: 11; GenBank Accession No. NM_004776), and the amino acid sequence of human B4GALT5 (e.g., SEQ ID NO: 12; UniProtKB Accession No. O43286) as well as B4GALT5 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "IL15RA" refers to Interleukin 15 Receptor Subunit Alpha and encompasses homologues, mutations, and isoforms thereof. IL15RA is also referred to in the art as CD215. The term encompasses full-length, unprocessed IL15RA, as well as any form of IL15RA that results from processing in the cell. The term encompasses naturally occurring variants of IL15RA (e.g., splice variants or allelic variants). The term encompasses, for example, the IL15RA gene, the mRNA sequence of human IL15RA (e.g., SEQ ID NO: 13; GenBank Accession No. NM_008358), and the amino acid sequence of human IL15RA (e.g., SEQ ID NO: 14; UniProtKB Accession No. Q13261) as well as IL15RA DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "TNFAIP3" refers to TNF alpha induced protein 3 and encompasses homologues, mutations, and isoforms thereof. TNFAIP3 is also referred to in the art as A20, OTUD7C, or AISBL. The term encompasses full-length, unprocessed TNFAIP3, as well as any form of TNFAIP3 that results from processing in the cell. The term encompasses naturally occurring variants of TNFAIP3 (e.g., splice variants or allelic variants). The term encompasses, for example, the TNFAIP3 gene, the mRNA sequence of human TNFAIP3 (e.g., SEQ ID NO: 15; GenBank Accession No. NM_001270508), and the amino acid sequence of human TNFAIP3 (e.g., SEQ ID NO: 16; UniProtKB Accession No. P21580) as well as TNFAIP3 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "SOCS1" refers to Suppressor Of Cytokine Signaling 1 and encompasses homologues, mutations, and isoforms thereof. SOCS1 is also referred to in the art as STAT-Induced STAT Inhibitor 1 (SSI1), Tec-Interacting Protein 3 (TIP3), Cytokine-Inducible SH2 Protein 1 (CISH1), or JAK Binding Protein. The term encompasses full-length, unprocessed SOCS1, as well as any form of SOCS1 that results from processing in the cell. The term encompasses naturally occurring variants of SOCS1 (e.g., splice variants or allelic variants). The term encompasses, for example, the SOCS1 gene, the mRNA sequence of human SOCS1 (e.g., SEQ ID NO: 17; GenBank Accession No. NM_003745), and the amino acid sequence of human SOCS1 (e.g., SEQ ID NO: 18; UniProtKB Accession No. O15524) as well as

SOCS1 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "IL1RN" refers to Interleukin 1 Receptor Antagonist and encompasses homologues, mutations, and isoforms thereof. IL1RN is also referred to in the art as Anakinra, IRAP, DIRA, or MVCD4. The term encompasses full-length, unprocessed IL1RN, as well as any form of IL1RN that results from processing in the cell. The term encompasses naturally occurring variants of IL1RN (e.g., splice variants or allelic variants). The term encompasses, for example, the IL1RN gene, the mRNA sequence of human IL1RN (e.g., SEQ ID NO: 19; GenBank Accession No. NM_173842), and the amino acid sequence of human IL1RN (e.g., SEQ ID NO: 20; UniProtKB Accession No. P18510) as well as IL1RN DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "PFKFB3" refers to 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3 and encompasses homologues, mutations, and isoforms thereof. PFKFB3 is also referred to in the art as IPFK2, PFK2, or iPFK-2. The term encompasses full-length, unprocessed PFKFB3, as well as any form of PFKFB3 that results from processing in the cell. The term encompasses naturally occurring variants of PFKFB3 (e.g., splice variants or allelic variants). The term encompasses, for example, the PFKFB3 gene, the mRNA sequence of human PFKFB3 (e.g., SEQ ID NO: 21; GenBank Accession No. NM_004566), and the amino acid sequence of human PFKFB3 (e.g., SEQ ID NO: 22; UniProtKB Accession No. Q16875) as well as PFKFB3 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "BCL2A1" refers to BCL2 Related Protein A1 and encompasses homologues, mutations, and isoforms thereof. BCL2A1 is also referred to in the art as GRS, ACC1, ACC2, BFL1, ACC-1, ACC-2, HBPA1, or BCL2L5. The term encompasses full-length, unprocessed BCL2A1, as well as any form of BCL2A1 that results from processing in the cell. The term encompasses naturally occurring variants of BCL2A1 (e.g., splice variants or allelic variants). The term encompasses, for example, the BCL2A1 gene, the mRNA sequence of human BCL2A1 (e.g., SEQ ID NO: 23; GenBank Accession No. NM_004049), and the amino acid sequence of human BCL2A1 (e.g., SEQ ID NO: 24; UniProtKB Accession No. Q16548) as well as BCL2A1 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "CXCL10" refers to C-X-C Motif Chemokine Ligand 10 and encompasses homologues, mutations, and isoforms thereof. CXCL10 is also referred to in the art as C7, IFI10, INP10, IP-10, crg-2, mob-1, SCYB10, or gIP-10. The term encompasses full-length, unprocessed CXCL10, as well as any form of CXCL10 that results from processing in the cell. The term encompasses naturally occurring variants of CXCL10 (e.g., splice variants or allelic variants). The term encompasses, for example, the CXCL10 gene, the mRNA sequence of human CXCL10 (e.g., SEQ ID NO: 25; GenBank Accession No. NM_001565), and the amino acid sequence of human CXCL10 (e.g., SEQ ID NO: 26; UniProtKB Accession No. P02778) as well as CXCL10 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "CCL8" refers to C-C Motif Chemokine Ligand 8 and encompasses homologues, mutations, and isoforms thereof. CCL8 is also referred to in the art as HC14, MCP2, MCP-2, SCYA8, or

SCYA10. The term encompasses full-length, unprocessed CCL8, as well as any form of CCL8 that results from processing in the cell. The term encompasses naturally occurring variants of CCL8 (e.g., splice variants or allelic variants). The term encompasses, for example, the CCL8 gene, the mRNA sequence of human CCL8 (e.g., SEQ ID NO: 27; GenBank Accession No. NM_005623), and the amino acid sequence of human CCL8 (e.g., SEQ ID NO: 28; UniProtKB Accession No. P80075) as well as CCL8 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "GPR84" refers to G Protein-Coupled Receptor 84 and encompasses homologues, mutations, and isoforms thereof. GPR84 is also referred to in the art as EX33 or GPCR4. The term encompasses full-length, unprocessed GPR84, as well as any form of GPR84 that results from processing in the cell. The term encompasses naturally occurring variants of GPR84 (e.g., splice variants or allelic variants). The term encompasses, for example, the GPR84 gene, the mRNA sequence of human GPR84 (e.g., SEQ ID NO: 29; GenBank Accession No. NM_020370), and the amino acid sequence of human GPR84 (e.g., SEQ ID NO: 30; UniProtKB Accession No. Q9NQS5) as well as GPR84 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "C15orf48" refers to Chromosome 15 Open Reading Frame 48 and encompasses homologues, mutations, and isoforms thereof. C15orf48 is also referred to in the art as NMES1 or FOAP-11. The term encompasses full-length, unprocessed C15orf48, as well as any form of C15orf48 that results from processing in the cell. The term encompasses naturally occurring variants of C15orf48 (e.g., splice variants or allelic variants). The term encompasses, for example, the C15orf48 gene, the mRNA sequence of human C15orf48 (e.g., SEQ ID NO: 31; GenBank Accession No. NM_197955), and the amino acid sequence of human C15orf48 (e.g., SEQ ID NO: 32; UniProtKB Accession No. Q9C002) as well as C15orf48 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "DRAM1" refers to DNA Damage Regulated Autophagy Modulator 1 and encompasses homologues, mutations, and isoforms thereof. DRAM1 is also referred to in the art as DRAM. The term encompasses full-length, unprocessed DRAM1, as well as any form of DRAM1 that results from processing in the cell. The term encompasses naturally occurring variants of DRAM1 (e.g., splice variants or allelic variants). The term encompasses, for example, the DRAM1 gene, the mRNA sequence of human DRAM1 (e.g., SEQ ID NO: 33; GenBank Accession No. NM_018370), and the amino acid sequence of human DRAM1 (e.g., SEQ ID NO: 34; UniProtKB Accession No. Q8N682) as well as DRAM1 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "CXCL11" refers to C-X-C Motif Chemokine Ligand 11 and encompasses homologues, mutations, and isoforms thereof. CXCL11 is also referred to in the art as IP9, H174, IP-9, b-R1, I-TAC, SCYB11, or SCYB9B. The term encompasses full-length, unprocessed CXCL11, as well as any form of CXCL11 that results from processing in the cell. The term encompasses naturally occurring variants of CXCL11 (e.g., splice variants or allelic variants). The term encompasses, for example, the CXCL11 gene, the mRNA sequence of human CXCL11 (e.g., SEQ ID NO: 35; GenBank Accession No.

NM_005409), and the amino acid sequence of human CXCL11 (e.g., SEQ ID NO: 36; UniProtKB Accession No. O14625) as well as CXCL11 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "TNFAIP6" refers to TNF Alpha Induced Protein 6 and encompasses homologues, mutations, and isoforms thereof. TNFAIP6 is also referred to in the art as TSG6 or TSG-6. The term encompasses full-length, unprocessed TNFAIP6, as well as any form of TNFAIP6 that results from processing in the cell. The term encompasses naturally occurring variants of TNFAIP6 (e.g., splice variants or allelic variants). The term encompasses, for example, the TNFAIP6 gene, the mRNA sequence of human TNFAIP6 (e.g., SEQ ID NO: 37; GenBank Accession No. NM_007115), and the amino acid sequence of human TNFAIP6 (e.g., SEQ ID NO: 38; UniProtKB Accession No. P98066) as well as TNFAIP6 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "CSRNP1" refers to Cysteine and Serine Rich Nuclear Protein 1 and encompasses homologues, mutations, and isoforms thereof. CSRNP1 is also referred to in the art as AXUD1, URAX1, TAIP-3, CSRNP-1, or FAM130B. The term encompasses full-length, unprocessed CSRNP1, as well as any form of CSRNP1 that results from processing in the cell. The term encompasses naturally occurring variants of CSRNP1 (e.g., splice variants or allelic variants). The term encompasses, for example, the CSRNP1 gene, the mRNA sequence of human CSRNP1 (e.g., SEQ ID NO: 39; GenBank Accession No. NM_033027), and the amino acid sequence of human CSRNP1 (e.g., SEQ ID NO: 40; UniProtKB Accession No. Q96S65) as well as CSRNP1 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "PLSCR1" refers to Phospholipid Scramblase 1 and encompasses homologues, mutations, and isoforms thereof. PLSCR1 is also referred to in the art as MMTRA1B. The term encompasses full-length, unprocessed PLSCR1, as well as any form of PLSCR1 that results from processing in the cell. The term encompasses naturally occurring variants of PLSCR1 (e.g., splice variants or allelic variants). The term encompasses, for example, the PLSCR1 gene, the mRNA sequence of human PLSCR1 (e.g., SEQ ID NO: 41; GenBank Accession No. NM_021105), and the amino acid sequence of human PLSCR1 (e.g., SEQ ID NO: 42; UniProtKB Accession No. O15162) as well as PLSCR1 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term "CLEC4E" refers to C-Type Lectin Domain Family 4 Member E and encompasses homologues, mutations, and isoforms thereof. CLEC4E is also referred to in the art as MINCLE or CLECSF9. The term encompasses full-length, unprocessed CLEC4E, as well as any form of CLEC4E that results from processing in the cell. The term encompasses naturally occurring variants of CLEC4E (e.g., splice variants or allelic variants). The term encompasses, for example, the CLEC4E gene, the mRNA sequence of human CLEC4E (e.g., SEQ ID NO: 43; GenBank Accession No. NM_014358), and the amino acid sequence of human CLEC4E (e.g., SEQ ID NO: 44; UniProtKB Accession No. Q9ULY5) as well as CLEC4E DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term “SAMSN1” refers to SAM Domain, SH3 Domain and Nuclear Localization Signals 1 and encompasses homologues, mutations, and isoforms thereof. SAMSN1 is also referred to in the art as SLy2, HACS1, NASH1, SASH2, or SH3D6B. The term encompasses full-length, unprocessed SAMSN1, as well as any form of SAMSN1 that results from processing in the cell. The term encompasses naturally occurring variants of SAMSN1 (e.g., splice variants or allelic variants). The term encompasses, for example, the SAMSN1 gene, the mRNA sequence of human SAMSN1 (e.g., SEQ ID NO: 45; GenBank Accession No. NM_022136), and the amino acid sequence of human SAMSN1 (e.g., SEQ ID NO: 46; UniProtKB Accession No. Q9NSI8) as well as SAMSN1 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

The term “ACSL1” refers to Acyl-CoA Synthetase Long-Chain Family Member 1 and encompasses homologues, mutations, and isoforms thereof. ACSL1 is also referred to in the art as Acs, Acas, FACS, Acas1, Facl2, or LACS1. The term encompasses full-length, unprocessed ACSL1, as well as any form of ACSL1that results from processing in the cell. The term encompasses naturally occurring variants of ACSL1 (e.g., splice variants or allelic variants). The term encompasses, for example, the ACSL1gene, the mRNA sequence of human ACSL1 (e.g., SEQ ID NO: 47; GenBank Accession No. NM_001286708), and the amino acid sequence of human ACSL1 (e.g., SEQ ID NO: 48; UniProtKB Accession No. P33121) as well as ACSL1 DNA, mRNA, and amino acid sequences from any other vertebrate source, including mammals such as primates and rodents (e.g., mice and rats).

As used herein, the terms “patient,” “individual,” and “subject” are used interchangeably and refer to any single animal, more preferably a mammal (including such non-human animals as, for example, cats, dogs, horses, rabbits, zoo animals, cows, pigs, sheep, and non-human primates) for which treatment is desired. In particular embodiments, the patient herein is a human. The patient may be a patient having, suspected of having, or at risk of suffering from an IRAK4-mediated disorder or condition (e.g., an immune disorder, an inflammatory disorder, a fibrotic disorder, an eosinophilic disorder, an infection, pain, a central nervous system disorder, an acute kidney injury, a chronic kidney disease, endometriosis, non-alcoholic fatty liver disease, a metabolic syndrome, and obesity). The patient may have been previously treated with an IRAK4 pathway inhibitor, another drug, or not previously treated. The patient may be naïve to an additional drug(s) being used when the treatment is started, i.e., the patient may not have been previously treated with, for example, a therapy other than one including an IRAK4 pathway inhibitor at “baseline” (i.e., at a set point in time before the administration of a first dose of an IRAK4 pathway inhibitor in the treatment method herein, such as the day of screening the subject before treatment is commenced). Such a “naïve” patient or subject is generally considered a candidate for treatment with such additional drug(s).

The term “antibody” herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen-binding activity.

“Polynucleotide” or “nucleic acid,” as used interchangeably herein, refers to polymers of nucleotides of any length and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be

incorporated into a polymer by DNA or RNA polymerase, or by a synthetic reaction. Thus, for instance, polynucleotides as defined herein include, without limitation, single- and double-stranded DNA, DNA including single- and double-stranded regions, single- and double-stranded RNA, and RNA including single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or include single- and double-stranded regions. In addition, the term "polynucleotide" as used herein refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The strands in such regions may be from the same molecule or from different molecules. The regions may include all of one or more of the molecules, but more typically involve only a region of some of the molecules. One of the molecules of a triple-helical region often is an oligonucleotide. The term "polynucleotide" specifically includes cDNAs.

A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after synthesis, such as by conjugation with a label. Other types of modifications include, for example, "caps," substitution of one or more of the naturally-occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, and the like) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, and the like), those containing pendant moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, and the like), those with intercalators (e.g., acridine, psoralen, and the like), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, and the like), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids), as well as unmodified forms of the polynucleotide(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to solid or semi-solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-, 2'-O-allyl-, 2'-fluoro-, or 2'-azido-ribose, carbocyclic sugar analogs, α-anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs, and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S ("thioate"), P(S)S ("dithioate"), $(O)NR_2$ ("amidate"), P(O)R, P(O)OR', CO or CH_2 ("formacetal"), in which each R or R' is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (-O-) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. A polynucleotide can contain one or more different types of modifications as described herein and/or multiple modifications of the same type. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.

"Oligonucleotide," as used herein, generally refers to short, single stranded, polynucleotides that are, but not necessarily, less than about 250 nucleotides in length. Oligonucleotides may be synthetic. The terms "oligonucleotide" and "polynucleotide" are not mutually exclusive. The description above for polynucleotides is equally and fully applicable to oligonucleotides.

The term "primer" refers to a single-stranded polynucleotide that is capable of hybridizing to a nucleic acid and allowing polymerization of a complementary nucleic acid, generally by providing a free 3'-OH group.

The term "small molecule" refers to any molecule with a molecular weight of about 2000 daltons or less, preferably of about 500 daltons or less.

The term "detection" includes any means of detecting, including direct and indirect detection.

The term "biomarker" as used herein refers to an indicator molecule or set of molecules (e.g., predictive, diagnostic, and/or prognostic indicator), which can be detected in a sample and includes, for example, CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, BCL2A1, CXCL10, CCL8, GPR84, C15orf48, DRAM1, CXCL11, TNFAIP6, CSRNP1, PLSCR1, CLEC4E, SAMSN1, and ACSL1. The biomarker may be a predictive biomarker and serve as an indicator of the likelihood of sensitivity or benefit of a patient having a particular disorder or condition (e.g., an IRAK4-mediated disorder or condition) to treatment with an IRAK4 pathway inhibitor. Biomarkers include, but are not limited to, polynucleotides (e.g., DNA and/or RNA (e.g., mRNA)), polynucleotide copy number alterations (e.g., DNA copy numbers), polypeptides, polypeptide and polynucleotide modifications (e.g., post-translational modifications), carbohydrates, and/or glycolipid-based molecular markers. In some embodiments, a biomarker is a gene.

The "amount" or "level" of a biomarker, as used herein, is a detectable level in a biological sample. These can be measured by methods known to one skilled in the art and also disclosed herein.

The term "expression level" or "level of expression" generally refers to the amount of a biomarker in a biological sample. "Expression" generally refers to the process by which information (e.g., gene-encoded and/or epigenetic information) is converted into the structures present and operating in the cell. Therefore, as used herein, "expression" may refer to transcription into a polynucleotide, translation into a polypeptide, or even polynucleotide and/or polypeptide modifications (e.g., posttranslational modification of a polypeptide). Fragments of the transcribed polynucleotide, the translated polypeptide, or polynucleotide and/or polypeptide modifications (e.g., posttranslational modification of a polypeptide) shall also be regarded as expressed whether they originate from a transcript generated by alternative splicing or a degraded transcript, or from a post-translational processing of the polypeptide, e.g., by proteolysis. "Expressed genes" include those that are transcribed into a polynucleotide as mRNA and then translated into a polypeptide, and also those that are transcribed into RNA but not translated into a polypeptide (for example, transfer and ribosomal RNAs).

"Increased expression," "increased expression level," "increased levels," "elevated expression," "elevated expression levels," or "elevated levels" refers to an increased expression or increased levels of a biomarker in an individual relative to a control, such as an individual or individuals who do not have the disorder or condition (e.g., an IRAK4-mediated disorder or condition) (e.g., healthy individuals), an

internal control (e.g., a housekeeping biomarker), or a median expression level of the biomarker in samples from a group/population of patients.

"Decreased expression," "decreased expression level," "decreased levels," "reduced expression," "reduced expression levels," or "reduced levels" refers to a decrease expression or decreased levels of a biomarker in an individual relative to a control, such as an individual or individuals who do not have a disorder or condition (e.g., an IRAK4-mediated disorder or condition) (e.g., healthy individuals), an internal control (e.g., a housekeeping biomarker), or a median expression level of the biomarker in samples from a group/population of patients. In some embodiments, reduced expression is little or no expression.

The term "housekeeping gene" refers herein to a gene or group of genes that encode proteins whose activities are essential for the maintenance of cell function and which are typically similarly present in all cell types.

"Amplification," as used herein generally refers to the process of producing multiple copies of a desired sequence. "Multiple copies" mean at least two copies. A "copy" does not necessarily mean perfect sequence complementarity or identity to the template sequence. For example, copies can include nucleotide analogs such as deoxyinosine, intentional sequence alterations (such as sequence alterations introduced through a primer comprising a sequence that is hybridizable, but not complementary, to the template), and/or sequence errors that occur during amplification.

The technique of "polymerase chain reaction" or "PCR" as used herein generally refers to a procedure wherein minute amounts of a specific piece of nucleic acid, RNA and/or DNA, are amplified as described, for example, in U.S. Pat. No. 4,683,195. Generally, sequence information from the ends of the region of interest or beyond needs to be available, such that oligonucleotide primers can be designed; these primers will be identical or similar in sequence to opposite strands of the template to be amplified. The 5' terminal nucleotides of the two primers may coincide with the ends of the amplified material. PCR can be used to amplify specific RNA sequences, specific DNA sequences from total genomic DNA, and cDNA transcribed from total cellular RNA, bacteriophage, or plasmid sequences, etc. See generally Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.* 51:263 (1987) and Erlich, ed., *PCR Technology*, (Stockton Press, NY, 1989). As used herein, PCR is considered to be one, but not the only, example of a nucleic acid polymerase reaction method for amplifying a nucleic acid test sample, comprising the use of a known nucleic acid (DNA or RNA) as a primer and utilizes a nucleic acid polymerase to amplify or generate a specific piece of nucleic acid or to amplify or generate a specific piece of nucleic acid which is complementary to a particular nucleic acid.

"Quantitative polymerase chain reaction" or "qPCR" refers to a form of PCR wherein the amount of PCR product is measured at each step in a PCR reaction. This technique has been described in various publications including, for example, Cronin et al., *Am. J. Pathol.* 164(1):35-42 (2004) and Ma et al., *Cancer Cell* 5:607-616 (2004).

The term "microarray" refers to an ordered arrangement of hybridizable array elements, preferably polynucleotide probes, on a substrate.

The term "sample," as used herein, refers to a composition that is obtained or derived from a subject (e.g., individual of interest) that contains a cellular and/or other molecular entity that is to be

characterized and/or identified, for example, based on physical, biochemical, chemical, and/or physiological characteristics. For example, the phrase "disease sample" and variations thereof refers to any sample obtained from a subject of interest that would be expected or is known to contain the cellular and/or molecular entity that is to be characterized. Samples include, but are not limited to, tissue samples, primary or cultured cells or cell lines, cell supernatants, cell lysates, platelets, serum, plasma, vitreous fluid, lymph fluid, synovial fluid, follicular fluid, seminal fluid, amniotic fluid, milk, whole blood, blood-derived cells, urine, cerebro-spinal fluid, saliva, sputum, tears, perspiration, mucus, tumor lysates, and tissue culture medium, tissue extracts such as homogenized tissue, tumor tissue, cellular extracts, and combinations thereof.

By "tissue sample" or "cell sample" is meant a collection of similar cells obtained from a tissue of a subject or individual. The source of the tissue or cell sample may be solid tissue as from a fresh, frozen and/or preserved organ, tissue sample, biopsy, and/or aspirate; blood or any blood constituents such as plasma; bodily fluids such as cerebral spinal fluid, amniotic fluid, peritoneal fluid, or interstitial fluid; cells from any time in gestation or development of the subject. The tissue sample may also be primary or cultured cells or cell lines. Optionally, the tissue or cell sample is obtained from a disease tissue/organ. For instance, a tumor sample is a tissue sample obtained from a tumor or other cancerous tissue.

A "reference sample," "reference cell," "reference tissue," "control sample," "control cell," or "control tissue," as used herein, refers to a sample, cell, tissue, standard, or level that is used for comparison purposes. In one embodiment, a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained from a healthy and/or non-diseased part of the body (e.g., tissue or cells) of the same subject or individual. For example, the reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue may be healthy and/or non-diseased cells or tissue adjacent to the diseased cells or tissue. In another embodiment, a reference sample is obtained from an untreated tissue and/or cell of the body of the same subject or individual. In yet another embodiment, a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained from a healthy and/or non-diseased part of the body (e.g., tissues or cells) of an individual who is not the subject or individual. In even another embodiment, a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained from an untreated tissue and/or cell of the body of an individual who is not the subject or individual.

For the purposes herein a "section" of a tissue sample is meant a single part or piece of a tissue sample, for example, a thin slice of tissue or cells cut from a tissue sample. It is to be understood that multiple sections of tissue samples may be taken and subjected to analysis, provided that it is understood that the same section of tissue sample may be analyzed at both morphological and molecular levels, or analyzed with respect to polypeptides (e.g., by immunohistochemistry) and/or polynucleotides (e.g., by *in situ* hybridization).

By "correlate" or "correlating" is meant comparing, in any way, the performance and/or results of a first analysis or protocol with the performance and/or results of a second analysis or protocol. For example, one may use the results of a first analysis or protocol in carrying out a second protocol and/or one may use the results of a first analysis or protocol to determine whether a second analysis or protocol

should be performed. With respect to the embodiment of polypeptide analysis or protocol, one may use the results of the polypeptide expression analysis or protocol to determine whether a specific therapeutic regimen should be performed. With respect to the embodiment of polynucleotide analysis or protocol, one may use the results of the polynucleotide expression analysis or protocol to determine whether a specific therapeutic regimen should be performed.

"Individual response" or "response" can be assessed using any endpoint indicating a benefit to the individual, including, without limitation, (1) inhibition, to some extent, of progression of IRAK4-mediated disorder or condition, including slowing down or complete arrest; (2) relief, to some extent, of one or more symptoms associated with the IRAK4-mediated disorder or condition; (6) increase or extension in the length of survival, including overall survival and progression-free survival; and/or (7) decreased mortality at a given point of time following treatment.

The term "survival" refers to the patient remaining alive, and includes overall survival as well as progression-free survival.

As used herein, "progression-free survival" or "PFS" refers to the length of time during and after treatment during which the disease being treated (e.g., an IRAK4-mediated disorder or condition (e.g., immune disorder (e.g., systemic lupus erythematosus (SLE)) or inflammatory disorder (e.g., asthma)) does not progress or get worse. Progression-free survival may include the amount of time individuals have experienced a complete response or a partial response, as well as the amount of time individuals have experienced stable disease.

As used herein, "overall survival" or "OS" refers to the percentage of subjects in a group who are likely to be alive after a particular duration of time (e.g., 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 10 years, 15 years, 20 years, or more than 20 years from the time of diagnosis or treatment).

An "effective response" of a patient or a patient's "responsiveness" to treatment with a medicament and similar wording refers to the clinical or therapeutic benefit imparted to a patient at risk for, or having, an IRAK4-mediated disorder or condition, such as an immune disorder (e.g., systemic lupus erythematosus (SLE)) or inflammatory disorder (e.g., asthma)). In one embodiment, one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 is used to identify a patient who is predicted to have an increased likelihood of being responsive to treatment with a medicament (e.g., treatment including an IRAK4 pathway inhibitor), relative to a patient who does not express the one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1. In one embodiment, one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 is used to identify the patient who is predicted to have an increase likelihood of being responsive to treatment with a medicament (e.g., treatment including an IRAK4 pathway inhibitor), relative to a patient who does not express the one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 at the same level.

A "disorder" is any condition that would benefit from treatment including, but not limited to, chronic and acute disorders or diseases, including those pathological conditions that predispose the mammal to the disorder in question.

The term “pharmaceutical formulation” refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

A “pharmaceutically acceptable excipient” refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable excipient includes, but is not limited to, a buffer, carrier, stabilizer, or preservative.

The term “pharmaceutically acceptable salt” denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts. The phrase “pharmaceutically acceptable” indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

The term “pharmaceutically acceptable acid addition salt” denotes those pharmaceutically acceptable salts formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids, such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid “mesylate”, ethanesulfonic acid, p-toluenesulfonic acid, and salicyclic acid.

The term “pharmaceutically acceptable base addition salt” denotes those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines, including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, and polyamine resins.

As used herein, “treatment” (and grammatical variations thereof such as “treat” or “treating”) refers to clinical intervention in an attempt to alter the natural course of the individual being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some embodiments, IRAK4 pathway inhibitors (e.g., IRAK4 inhibitors, IRAK1 inhibitors, toll-like receptor (TLR) inhibitors, interleukin-1 receptor (IL-1R) inhibitors, interleukin-33 receptor (IL-33R) inhibitors, or myeloid differentiation primary response gene 88 (MyD88)

inhibitors) are used to delay development of an IRAK4-mediated disorder or condition or to slow the progression of an IRAK4-mediated disorder or condition.

As used herein, "administering" is meant a method of giving a dosage of a compound (e.g., an IRAK4 pathway inhibitor, such as an IRAK4 inhibitor or antagonist) or a pharmaceutical composition (e.g., a pharmaceutical composition including an inhibitor or antagonist) to a subject (e.g., a patient). Administering can be by any suitable means, including parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include, for example, intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing can be by any suitable route, e.g., by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. Various dosing schedules including but not limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion are contemplated herein.

The term "co-administered" is used herein to refer to administration of two or more therapeutic agents, where at least part of the administration overlaps in time. Accordingly, concurrent administration includes a dosing regimen when the administration of one or more agent(s) continues after discontinuing the administration of one or more other agent(s).

By "reduce or inhibit" is meant the ability to cause an overall decrease of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or greater. Reduce or inhibit can refer, for example, to the level of activity and/or function of a protein in the IRAK4 pathway (e.g., the level of signal transduction through the IRAK4 pathway). Additionally, reduce or inhibit can refer, for example, to the symptoms of the disorder or condition being treated (e.g., an IRAK4-mediated disorder or condition).

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, combination therapy, contraindications, and/or warnings concerning the use of such therapeutic products.

An "article of manufacture" is any manufacture (e.g., a package or container) or kit comprising at least one reagent, e.g., a medicament for treatment of a disease or disorder (e.g., an IRAK4-mediated disorder or condition), or a probe for specifically detecting a biomarker (e.g., CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, BCL2A1, CXCL10, CCL8, GPR84, C15orf48, DRAM1, CXCL11, TNFAIP6, CSRNP1, PLSCR1, CLEC4E, SAMSN1, and/or ACSL1) described herein. In certain embodiments, the manufacture or kit is promoted, distributed, or sold as a unit for performing the methods described herein.

The phrase "based on" when used herein means that the information about one or more biomarkers is used to inform a diagnostic decision, a treatment decision, information provided on a package insert, or marketing/promotional guidance, etc.

III. Methods

A. Diagnostic Methods Based on the Expression Level of IRAK4 Pathway Biomarkers

The present invention provides diagnostic methods in which the IRAK4 pathway biomarkers identified herein serve as pharmacodynamic biomarkers.

Accordingly, the present invention features diagnostic methods of monitoring the response of a patient having an interleukin-1 receptor-associated kinase 4 (IRAK4)-mediated disorder or condition to treatment including an IRAK4 pathway inhibitor, the method including (a) determining, in a sample obtained from the patient at a time point following administration of a first dose of the IRAK4 pathway inhibitor, the expression level of one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 below, and (b) comparing the expression level of the one or more genes set forth in Table 1 in the sample with a reference expression level, thereby monitoring the response of the patient to treatment including the IRAK4 pathway inhibitor.

Table 1. IRAK4 Pathway Biomarker Genes

Genes
CD38
SOCS3
AQP9
CDKN1A
GADD45B
B4GALT5
IL15RA
TNFAIP3
SOCS1
IL1RN
PFKFB3
BCL2A1
CXCL10
CCL8
GPR84
C15orf48
DRAM1
CXCL11
TNFAIP6
CSRNP1
PLSCR1
CLEC4E
SAMSN1
ACSL1

Accordingly, one could determine the expression levels of any combination of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, or 23 genes selected from the genes set forth in Table 1 in a sample obtained from the patient at a time point following administration of a first dose of the IRAK4

pathway inhibitor and, subsequently, compare the expression levels of the combination of genes with a reference expression level (e.g., the median expression levels of the same combination of genes in a reference population of individuals), thereby monitoring the response of the patient to treatment including the IRAK4 pathway inhibitor.

In certain instances, the method includes determining, in a sample obtained from the patient at a time point following administration of a first dose of the IRAK4 pathway inhibitor, the expression level of one or more genes (e.g., one gene, two genes, three genes, four genes, five genes, six genes, seven genes, eight genes, nine genes, ten genes, eleven genes, or all twelve genes) selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1. For example, in some instances, the method includes determining, in a sample obtained from the patient at a time point following administration of a first dose of the IRAK4 pathway inhibitor, the expression level of one or more genes (e.g., one gene, two genes, three genes, four genes, five genes, six genes, seven genes, eight genes, nine genes, ten genes, or all eleven genes) selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3. In particular instances, the method includes determining, in a sample obtained from the patient at a time point following administration of a first dose of the IRAK4 pathway inhibitor, the expression level of one or more genes (e.g., one gene, two genes, three genes, four genes, five genes, six genes, seven genes, eight genes, or all nine genes) selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1.

In some instances, the expression level of the one or more genes set forth in Table 1 is decreased in the sample obtained from the patient at a time point following administration of a first dose of the IRAK4 pathway inhibitor relative to the reference expression level. For example, in some instances, the expression level of the one or more genes set forth in Table 1 is decreased by about 1% or more (e.g., about 2% or more, about 3% or more, about 4% or more, about 5% or more, about 6% or more, about 7% or more, about 8% or more, about 9% or more, about 10% or more, about 11% or more, about 12% or more, about 13% or more, about 14% or more, about 15% or more, about 20% or more, about 25% or more, about 30% or more, about 35% or more, about 40% or more, about 45% or more, about 50% or more, about 55% or more, about 60% or more, about 65% or more, about 70% or more, about 75% or more, about 80% or more, about 85% or more, about 90% or more, about 95% or more, or about 100%), e.g., from about 1% to about 5%, from about 5% to about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 35%, from about 35% to about 40%, from about 40% to about 45%, from about 45% to about 50%, from about 50% to about 55%, from about 55% to about 60%, from about 60% to about 65%, from about 65% to about 70%, from about 70% to about 75%, from about 75% to about 80%, from about 80% to about 85%, from about 85% to about 90%, from about 90% to about 95%, or from about 95% to about 100%, relative to a reference expression level (e.g., the expression level of the one or more genes set forth in Table 1 in a sample from the patient obtained prior to administration of the first dose of the IRAK4 pathway inhibitor). In other instances, the expression level of the one or more genes set forth in Table 1 is decreased by about 0.5-fold, about 0.6-fold, about 0.7-fold, about 0.8-fold, about 0.9-fold, about 1-fold, about 1.1-fold, about 1.2-fold, about 1.3-fold, about 1.4-fold, about 1.5-fold, about 1.6-fold,

about 1.7-fold, about 1.8-fold, about 1.9-fold, about 2-fold, about 2.1-fold, about 2.2-fold, about 2.3-fold, about 2.4-fold, about 2.5-fold, about 3-fold, about 3.5-fold, about 4-fold, about 4.5-fold, about 5-fold, about 5.5-fold, about 6-fold, about 6.5-fold, about 7-fold, about 7.5-fold, about 8-fold, about 8.5-fold, about 9-fold, about 9.5-fold, or about 10-fold or greater, e.g., from about 0.5-fold to about 0.7-fold, from about 0.7-fold to about 1-fold, from about 1-fold to about 1.5-fold, from about 1.5-fold to about 2-fold, from about 2-fold to about 3-fold, from about 3-fold to about 4-fold, from about 4-fold to about 5-fold, from about 5-fold to about 6-fold, from about 6-fold to about 7-fold, from about 7-fold to about 8-fold, or from about 9-fold to about 10-fold or greater, relative to the reference expression level (e.g., the expression level of the one or more genes set forth in Table 1 in a sample from the patient obtained prior to administration of the first dose of the IRAK4 pathway inhibitor).

In some embodiments, reduced or decreased expression refers to an overall reduction of about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or greater, in the level of biomarker (e.g., protein or nucleic acid (e.g., gene or mRNA)), detected by standard art known methods such as those described herein, as compared to a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. In certain embodiments, reduced expression refers to the decrease in expression level (amount) of a biomarker in the sample wherein the decrease is at least about any of 0.9x, 0.8x, 0.7x, 0.6x, 0.5x, 0.4x, 0.3x, 0.2x, 0.1x, 0.05x, or 0.01x the expression level (amount) of the respective biomarker in a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue.

In any one the preceding embodiments, the decreased expression level of the one or more genes set forth in Table 1 may indicate that the patient is responding to the IRAK4 pathway inhibitor. Accordingly, in some instances, the method further includes administering at least a second dose (e.g., one, two, three, four, five, six, seven, eight, nine, or ten or more additional doses) of an IRAK4 pathway inhibitor to a patient whose expression level of the one or more genes set forth in Table 1 is decreased relative to the reference expression level.

In any one the preceding embodiments, the reference expression level can be: (i) the expression level of the one or more genes set forth in Table 1 in a sample from the patient obtained prior to administration of the first dose of the IRAK4 pathway inhibitor; (ii) the expression level of the one or more genes set forth in Table 1 in a reference population (e.g., a median expression level of the one or more genes set forth in Table 1 in a reference population); (iii) a pre-assigned expression level for the one or more genes set forth in Table 1; (iv) the expression level of the one or more genes set forth in Table 1 in a sample obtained from the patient at a previous time point, wherein the previous time point is following administration of the first dose of the IRAK4 pathway inhibitor; or (v) the expression level of the one or more genes set forth in Table 1 in a sample obtained from the patient at a subsequent time point.

The present invention provides diagnostic methods in which the IRAK4 pathway biomarkers identified herein serve as predictive biomarkers.

Accordingly, the present invention features diagnostic methods of identifying a patient having an IRAK4-mediated disorder or condition who may benefit from treatment comprising an IRAK4 pathway inhibitor, the method including determining an expression level of one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 in a

sample obtained from the patient, wherein an increased expression level of the one or more genes set forth in Table 1 in the sample as compared to a reference expression level identifies the patient as one who may benefit from treatment including an IRAK4 pathway inhibitor.

The present invention also features diagnostic methods of selecting a therapy for a patient having an IRAK4-mediated disorder or condition, the method including determining an expression level of one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 in a sample obtained from the patient, wherein an increased expression level of the one or more genes set forth in Table 1 in the sample as compared to a reference expression level identifies the patient as one who may benefit from treatment including an IRAK4 pathway inhibitor.

In certain instances, the methods of identifying a patient or selecting a therapy for a patient may include determining the expression level of one or more genes (e.g., one gene, two genes, three genes, four genes, five genes, six genes, seven genes, eight genes, nine genes, ten genes, eleven genes, or all twelve genes) selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1. For example, in some instances, the method includes determining the expression level of one or more genes (e.g., one gene, two genes, three genes, four genes, five genes, six genes, seven genes, eight genes, nine genes, ten genes, or all eleven genes) selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3. In particular instances, the method includes determining the expression level of one or more genes (e.g., one gene, two genes, three genes, four genes, five genes, six genes, seven genes, eight genes, or all nine genes) selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1.

In some instances, the expression level of one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 is increased in the sample obtained from the patient relative to the reference expression level. For example, in some instances, the expression level of the one or more genes set forth in Table 1 is increased by about 1% or more (e.g., about 2% or more, about 3% or more, about 4% or more, about 5% or more, about 6% or more, about 7% or more, about 8% or more, about 9% or more, about 10% or more, about 11% or more, about 12% or more, about 13% or more, about 14% or more, about 15% or more, about 20% or more, about 25% or more, about 30% or more, about 35% or more, about 40% or more, about 45% or more, about 50% or more, about 55% or more, about 60% or more, about 65% or more, about 70% or more, about 75% or more, about 80% or more, about 85% or more, about 90% or more, about 95% or more, or about 100%), e.g., from about 1% to about 5%, from about 5% to about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 35%, from about 35% to about 40%, from about 40% to about 45%, from about 45% to about 50%, from about 50% to about 55%, from about 55% to about 60%, from about 60% to about 65%, from about 65% to about 70%, from about 70% to about 75%, from about 75% to about 80%, from about 80% to about 85%, from about 85% to about 90%, from about 90% to about 95%, or from about 95% to about 100%, relative to a reference expression level (e.g., the expression level of the one or more genes set forth in Table 1 in a reference population, e.g., a median expression level of the one or more genes set forth in Table 1 in a reference population). In other instances, the expression level of the one

or more genes set forth in Table 1 is increased by about 0.5-fold, about 0.6-fold, about 0.7-fold, about 0.8-fold, about 0.9-fold, about 1-fold, about 1.1-fold, about 1.2-fold, about 1.3-fold, about 1.4-fold, about 1.5-fold, about 1.6-fold, about 1.7-fold, about 1.8-fold, about 1.9-fold, about 2-fold, about 2.1-fold, about 2.2-fold, about 2.3-fold, about 2.4-fold, about 2.5-fold, about 3-fold, about 3.5-fold, about 4-fold, about 4.5-fold, about 5-fold, about 5.5-fold, about 6-fold, about 6.5-fold, about 7-fold, about 7.5-fold, about 8-fold, about 8.5-fold, about 9-fold, about 9.5-fold, or about 10-fold or greater, e.g., from about 0.5-fold to about 0.7-fold, from about 0.7-fold to about 1-fold, from about 1-fold to about 1.5-fold, from about 1.5-fold to about 2-fold, from about 2-fold to about 3-fold, from about 3-fold to about 4-fold, from about 4-fold to about 5-fold, from about 5-fold to about 6-fold, from about 6-fold to about 7-fold, from about 7-fold to about 8-fold, or from about 9-fold to about 10-fold or greater, relative to the reference expression level (e.g., e.g., the expression level of the one or more genes set forth in Table 1 in a reference population, e.g., a median expression level of the one or more genes set forth in Table 1 in a reference population). In some embodiments, elevated or increased expression refers to an overall increase of about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or greater, in the level of biomarker (e.g., protein or nucleic acid (e.g., gene or mRNA)), detected by standard art-known methods such as those described herein, as compared to a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue.

In certain embodiments, the elevated or increased expression refers to the increase in expression level (amount) of a biomarker in the sample, wherein the increase is at least about any of 1.5x, 1.75x, 2x, 3x, 4x, 5x, 6x, 7x, 8x, 9x, 10x, 25x, 50x, 75x, or 100x the expression level (amount) of the respective biomarker in a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. In some embodiments, elevated expression refers to an overall increase of greater than about 1.5-fold, about 1.75-fold, about 2-fold, about 2.25-fold, about 2.5-fold, about 2.75-fold, about 3.0-fold, or about 3.25-fold as compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (e.g., housekeeping gene). In some instances, the patient has an increased expression level of the one or more genes set forth in Table 1 relative to the reference expression level and the method further comprises administering to the patient an IRAK4 pathway inhibitor.

In some embodiments, the reference expression level can be: (i) the expression level of the one or more genes set forth in Table 1 in a reference population (e.g., a median expression level of the one or more genes set forth in Table 1 in a reference population); or (ii) a pre-assigned expression level for the one or more genes set forth in Table 1.

The diagnostic methods described above provide for convenient, efficient, and potentially cost-effective means to obtain data and information useful in assessing appropriate or effective therapies for treating patients. For example, the sample obtained from the patient can be a tissue sample, a whole blood sample, a plasma sample, or a serum sample. A patient can the sample before and/or after treatment with an IRAK4 pathway inhibitor, and the sample can be examined by way of various in vitro assays to determine whether the patient will likely benefit from treatment including an IRAK4 pathway inhibitor, such as an IRAK4 inhibitor, an IRAK1 inhibitor, a toll-like receptor (TLR) inhibitor, an interleukin-

1 receptor (IL-1R) inhibitor, an interleukin-33 receptor (IL-33R) inhibitor, or a myeloid differentiation primary response gene 88 (MyD88) inhibitor.

In another aspect, the invention also provides methods for monitoring the sensitivity of a patient to an IRAK4 pathway inhibitor. The methods may be conducted in a variety of assay formats, including assays detecting genetic or protein expression levels and biochemical assays detecting appropriate activity. Determination of expression or the presence of such biomarkers in patient samples is predictive of whether a patient is sensitive to the biological effects of an IRAK4 pathway inhibitor. A difference or change (i.e., a decrease) in the expression of one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 in a sample obtained from the patient at a time point following administration of a first dose of the IRAK4 pathway inhibitor relative to a reference level (e.g., the expression level of the one or more genes set forth in Table 1 in a sample from the patient obtained prior to administration of the first dose of the IRAK4 pathway inhibitor, the median expression level of the one or more genes in a sample from a group/population of patients being tested for sensitivity to the IRAK4 pathway inhibitor, or the median expression level of the one or more genes in a sample from a group/population of patients having a particular IRAK4-mediated disorder or condition) correlates with treatment efficacy of such a patient with an IRAK4 pathway inhibitor.

In another aspect, the invention provides a method of optimizing therapeutic efficacy of therapy for a patient having a IRAK4-mediated disorder or condition, including detecting, one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 in a sample from the patient obtained (i) before an IRAK4 pathway inhibitor has been administered to the patient, (ii) after an IRAK4 pathway signaling inhibitor has been administered to the patient, or (iii) before and after such treatment. An increased expression level of one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 in a sample obtained before an IRAK4 pathway inhibitor has been administered to the patient indicates that the patient will likely benefit from treatment including an IRAK4 pathway inhibitor, and the therapy for the patient having the IRAK4-mediated disorder or condition may be accordingly adjusted to include an IRAK4 pathway inhibitor. In other instances, a decreased expression level, relative to a reference expression level, of the one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 following administration of the IRAK4 pathway indicates that the patient is responding to treatment with the IRAK4 pathway inhibitor, and treatment may optionally be continued, adjusted, or stopped accordingly. The patient may be informed that they have an increased likelihood of responding to treatment including an IRAK4 pathway inhibitor and/or provided a recommendation that treatment include an IRAK4 pathway inhibitor.

In any of the methods described herein, one could determine the expression levels of any combination of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 genes selected from the genes set forth in Table 1 in a sample obtained from the patient.

In some embodiments of the diagnostic methods described herein, the expression levels of a combination of two genes set forth in Table 1, such as any of the exemplary combinations shown in Table 2, may be determined.

Table 2. Exemplary Two-Gene Combinations of IRAK4 Biomarkers

CD38 and SOCS3
CD38 and AQP9
CD38 and CDKN1A
CD38 and GADD45B
CD38 and B4GALT5
CD38 and IL15RA
CD38 and TNFAIP3
CD38 and SOCS1
SOCS3 and AQP9
SOCS3 and CDKN1A
SOCS3 and GADD45B
SOCS3 and B4GALT5
SOCS3 and IL15RA
SOCS3 and TNFAIP3
SOCS3 and SOCS1
AQP9 and CDKN1A
AQP9 and GADD45B
AQP9 and B4GALT5
AQP9 and IL15RA
AQP9 and TNFAIP3
AQP9 and SOCS1
CDKN1A and GADD45B
CDKN1A and B4GALT5
CDKN1A and IL15RA
CDKN1A and TNFAIP3
CDKN1A and SOCS1
GADD45B and B4GALT5
GADD45B and IL15RA
GADD45B and TNFAIP3
GADD45B and SOCS1
B4GALT5 and IL15RA
B4GALT5 and TNFAIP3
B4GALT5 and SOCS1
IL15RA and TNFAIP3
IL15RA and SOCS1
TNFAIP3 and SOCS1

In some embodiments of the diagnostic methods described herein, the expression levels of a combination of three genes set forth in Table 1, such as any of the exemplary combinations shown in Table 3, may be determined.

Table 3. Exemplary Three-Gene Combinations of IRAK4 Biomarkers

CD38, SOCS3, and AQP9
CD38, SOCS3, and CDKN1A
CD38, SOCS3, and GADD45B
CD38, SOCS3, and B4GALT5
CD38, SOCS3, and IL15RA
CD38, SOCS3, and TNFAIP3
CD38, SOCS3, and SOCS1

CD38, AQP9, and CDKN1A
CD38, AQP9, and GADD45B
CD38, AQP9, and B4GALT5
CD38, AQP9, and IL15RA
CD38, AQP9, and TNFAIP3
CD38, AQP9, and SOCS1
CD38, CDKN1A, and GADD45B
CD38, CDKN1A, and B4GALT5
CD38, CDKN1A, and IL15RA
CD38, CDKN1A, and TNFAIP3
CD38, CDKN1A, and SOCS1
CD38, GADD45B, and B4GALT5
CD38, GADD45B, and IL15RA
CD38, GADD45B, and TNFAIP3
CD38, GADD45B, and SOCS1
CD38, B4GALT5, and IL15RA
CD38, B4GALT5, and TNFAIP3
CD38, B4GALT5, and SOCS1
CD38, IL15RA, and TNFAIP3
CD38, IL15RA, and SOCS1
CD38, TNFAIP3, and SOCS1
SOCS3, AQP9, and CDKN1A
SOCS3, AQP9, and GADD45B
SOCS3, AQP9, and B4GALT5
SOCS3, AQP9, and IL15RA
SOCS3, AQP9, and TNFAIP3
SOCS3, AQP9, and SOCS1
SOCS3, CDKN1A, and GADD45B
SOCS3, CDKN1A, and B4GALT5
SOCS3, CDKN1A, and IL15RA
SOCS3, CDKN1A, and TNFAIP3
SOCS3, CDKN1A, and SOCS1
SOCS3, GADD45B, and B4GALT5
SOCS3, GADD45B, and IL15RA
SOCS3, GADD45B, and TNFAIP3
SOCS3, GADD45B, and SOCS1
SOCS3, B4GALT5, and IL15RA
SOCS3, B4GALT5, and TNFAIP3
SOCS3, B4GALT5, and SOCS1
SOCS3, IL15RA, and TNFAIP3
SOCS3, IL15RA, and SOCS1
SOCS3, TNFAIP3, and SOCS1
AQP9, CDKN1A, and GADD45B
AQP9, CDKN1A, and B4GALT5
AQP9, CDKN1A, and IL15RA
AQP9, CDKN1A, and TNFAIP3
AQP9, CDKN1A, and SOCS1
AQP9, GADD45B, and B4GALT5
AQP9, GADD45B, and IL15RA
AQP9, GADD45B, and TNFAIP3
AQP9, GADD45B, and SOCS1
AQP9, B4GALT5, and IL15RA

AQP9, B4GALT5, and TNFAIP3
AQP9, B4GALT5, and SOCS1
AQP9, IL15RA, and TNFAIP3
AQP9, IL15RA, and SOCS1
AQP9, TNFAIP3, and SOCS1
CDKN1A, GADD45B, and B4GALT5
CDKN1A, GADD45B, and IL15RA
CDKN1A, GADD45B, and TNFAIP3
CDKN1A, GADD45B, and SOCS1
CDKN1A, B4GALT5, and IL15RA
CDKN1A, B4GALT5, and TNFAIP3
CDKN1A, B4GALT5, and SOCS1
CDKN1A, IL15RA, and TNFAIP3
CDKN1A, IL15RA, and SOCS1
CDKN1A, TNFAIP3, and SOCS1
GADD45B, B4GALT5, and IL15RA
GADD45B, B4GALT5, and TNFAIP3
GADD45B, B4GALT5, and SOCS1
GADD45B, IL15RA, and TNFAIP3
GADD45B, IL15RA, and SOCS1
GADD45B, TNFAIP3, and SOCS1
B4GALT5, IL15RA, and TNFAIP3
B4GALT5, IL15RA, and SOCS1
B4GALT5, TNFAIP3, and SOCS1
IL15RA, TNFAIP3, and SOCS1

In some embodiments of the diagnostic methods described herein, the expression levels of a combination of four genes set forth in Table 1, such as any of the exemplary combinations shown in Table 4, may be determined.

5

Table 4. Exemplary Four-Gene Combinations of IRAK4 Biomarkers

CD38, SOCS3, AQP9, and CDKN1A
CD38, SOCS3, AQP9, and GADD45B
CD38, SOCS3, AQP9, and B4GALT5
CD38, SOCS3, AQP9, and IL15RA
CD38, SOCS3, AQP9 , and TNFAIP3
CD38, SOCS3, AQP9, and SOCS1
CD38, SOCS3, CDKN1A, and GADD45B
CD38, SOCS3, CDKN1A, and B4GALT5
CD38, SOCS3, CDKN1A, and IL15RA
CD38, SOCS3, CDKN1A, and TNFAIP3
CD38, SOCS3, CDKN1A, and SOCS1
CD38, SOCS3, GADD45B, and B4GALT5
CD38, SOCS3, GADD45B, and IL15RA
CD38, SOCS3, GADD45B, and TNFAIP3
CD38, SOCS3, GADD45B, and SOCS1
CD38, SOCS3, B4GALT5, and IL15RA
CD38, SOCS3, B4GALT5, and TNFAIP3
CD38, SOCS3, B4GALT5, and SOCS1
CD38, SOCS3, IL15RA, and TNFAIP3

CD38, SOCS3, IL15RA, and SOCS1
CD38, SOCS3, TNFAIP3, and SOCS1
CD38, AQP9, CDKN1A, and GADD45B
CD38, AQP9, CDKN1A, and B4GALT5
CD38, AQP9, CDKN1A, and IL15RA
CD38, AQP9, CDKN1A, and TNFAIP3
CD38, AQP9, CDKN1A, and SOCS1
CD38, AQP9, GADD45B, and B4GALT5
CD38, AQP9, GADD45B, and IL15RA
CD38, AQP9, GADD45B, and TNFAIP3
CD38, AQP9, GADD45B, and SOCS1
CD38, AQP9, B4GALT5, and IL15RA
CD38, AQP9, B4GALT5, and TNFAIP3
CD38, AQP9, B4GALT5, and SOCS1
CD38, AQP9, IL15RA, and TNFAIP3
CD38, AQP9, IL15RA, and SOCS1
CD38, AQP9, TNFAIP3, and SOCS1
CD38, CDKN1A, GADD45B, and B4GALT5
CD38, CDKN1A, GADD45B, and IL15RA
CD38, CDKN1A, GADD45B, and TNFAIP3
CD38, CDKN1A, GADD45B, and SOCS1
CD38, CDKN1A, B4GALT5, and IL15RA
CD38, CDKN1A, B4GALT5, and TNFAIP3
CD38, CDKN1A, B4GALT5, and SOCS1
CD38, CDKN1A, IL15RA, and TNFAIP3
CD38, CDKN1A, IL15RA, and SOCS1
CD38, CDKN1A, TNFAIP3, and SOCS1
CD38, GADD45B, B4GALT5, and IL15RA
CD38, GADD45B, B4GALT5, and TNFAIP3
CD38, GADD45B, B4GALT5, and SOCS1
CD38, GADD45B, IL15RA, and TNFAIP3
CD38, GADD45B, IL15RA, and SOCS1
CD38, GADD45B, TNFAIP3, and SOCS1
CD38, B4GALT5, IL15RA, and TNFAIP3
CD38, B4GALT5, IL15RA, and SOCS1
CD38, B4GALT5, TNFAIP3, and SOCS1
CD38, IL15RA, TNFAIP3, and SOCS1
SOCS3, AQP9, CDKN1A, and GADD45B
SOCS3, AQP9, CDKN1A, and B4GALT5
SOCS3, AQP9, CDKN1A, and IL15RA
SOCS3, AQP9, CDKN1A, and TNFAIP3
SOCS3, AQP9, CDKN1A, and SOCS1
SOCS3, AQP9, GADD45B, and B4GALT5
SOCS3, AQP9, GADD45B, and IL15RA
SOCS3, AQP9, GADD45B, and TNFAIP3
SOCS3, AQP9, GADD45B, and SOCS1
SOCS3, AQP9, B4GALT5, and IL15RA
SOCS3, AQP9, B4GALT5, and TNFAIP3
SOCS3, AQP9, B4GALT5, and SOCS1
SOCS3, AQP9, IL15RA, and TNFAIP3
SOCS3, AQP9, IL15RA, and SOCS1
SOCS3, AQP9, TNFAIP3, and SOCS1

SOCS3, CDKN1A, GADD45B, and B4GALT5
SOCS3, CDKN1A, GADD45B, and IL15RA
SOCS3, CDKN1A, GADD45B, and TNFAIP3
SOCS3, CDKN1A, GADD45B, and SOCS1
SOCS3, CDKN1A, B4GALT5, and IL15RA
SOCS3, CDKN1A, B4GALT5, and TNFAIP3
SOCS3, CDKN1A, B4GALT5, and SOCS1
SOCS3, CDKN1A, IL15RA, and TNFAIP3
SOCS3, CDKN1A, IL15RA, and SOCS1
SOCS3, CDKN1A, TNFAIP3, and SOCS1
SOCS3, GADD45B, B4GALT5, and IL15RA
SOCS3, GADD45B, B4GALT5, and TNFAIP3
SOCS3, GADD45B, B4GALT5, and SOCS1
SOCS3, GADD45B, IL15RA, and TNFAIP3
SOCS3, GADD45B, IL15RA, and SOCS1
SOCS3, GADD45B, TNFAIP3, and SOCS1
SOCS3, B4GALT5, IL15RA, and TNFAIP3
SOCS3, B4GALT5, IL15RA, and SOCS1
SOCS3, B4GALT5, TNFAIP3, and SOCS1
SOCS3, IL15RA, TNFAIP3, and SOCS1
AQP9, CDKN1A, GADD45B, and B4GALT5
AQP9, CDKN1A, GADD45B, and IL15RA
AQP9, CDKN1A, GADD45B, and TNFAIP3
AQP9, CDKN1A, GADD45B, and SOCS1
AQP9, CDKN1A, B4GALT5, and IL15RA
AQP9, CDKN1A, B4GALT5, and TNFAIP3
AQP9, CDKN1A, B4GALT5, and SOCS1
AQP9, CDKN1A, IL15RA, and TNFAIP3
AQP9, CDKN1A, IL15RA, and SOCS1
AQP9, CDKN1A, TNFAIP3, and SOCS1
AQP9, GADD45B, B4GALT5, and IL15RA
AQP9, GADD45B, B4GALT5, and TNFAIP3
AQP9, GADD45B, B4GALT5, and SOCS1
AQP9, GADD45B, IL15RA, and TNFAIP3
AQP9, GADD45B, IL15RA, and SOCS1
AQP9, GADD45B, TNFAIP3, and SOCS1
AQP9, B4GALT5, IL15RA, and TNFAIP3
AQP9, B4GALT5, IL15RA, and SOCS1
AQP9, B4GALT5, TNFAIP3, and SOCS1
AQP9, IL15RA, TNFAIP3, and SOCS1
CDKN1A, GADD45B, B4GALT5, and IL15RA
CDKN1A, GADD45B, B4GALT5, and TNFAIP3
CDKN1A, GADD45B, B4GALT5, and SOCS1
CDKN1A, GADD45B, IL15RA, and TNFAIP3
CDKN1A, GADD45B, IL15RA, and SOCS1
CDKN1A, GADD45B, TNFAIP3, and SOCS1
CDKN1A, B4GALT5, IL15RA, and TNFAIP3
CDKN1A, B4GALT5, IL15RA, and SOCS1
CDKN1A, B4GALT5, TNFAIP3, and SOCS1
CDKN1A, IL15RA, TNFAIP3, and SOCS1
GADD45B, B4GALT5, IL15RA, and TNFAIP3
GADD45B, B4GALT5, IL15RA, and SOCS1

GADD45B, B4GALT5, TNFAIP3, and SOCS1
GADD45B, IL15RA, TNFAIP3, and SOCS1
B4GALT5, IL15RA, TNFAIP3, and SOCS1

In some embodiments of the diagnostic methods described herein, the expression levels of a combination of five genes set forth in Table 1, such as any of the exemplary combinations shown in Table 5, may be determined.

Table 5. Exemplary Five-Gene Combinations of IRAK4 Biomarkers

CD38, SOCS3, AQP9, CDKN1A, and GADD45B
CD38, SOCS3, AQP9, CDKN1A, and B4GALT5
CD38, SOCS3, AQP9, CDKN1A, and IL15RA
CD38, SOCS3, AQP9, CDKN1A, and TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, and SOCS1
CD38, SOCS3, AQP9, GADD45B, and B4GALT5
CD38, SOCS3, AQP9, GADD45B, and IL15RA
CD38, SOCS3, AQP9, GADD45B, and TNFAIP3
CD38, SOCS3, AQP9, GADD45B, and SOCS1
CD38, SOCS3, AQP9, B4GALT5, and IL15RA
CD38, SOCS3, AQP9, B4GALT5, and TNFAIP3
CD38, SOCS3, AQP9, B4GALT5, and SOCS1
CD38, SOCS3, AQP9, IL15RA, and TNFAIP3
CD38, SOCS3, AQP9, IL15RA, and SOCS1
CD38, SOCS3, AQP9, TNFAIP3, and SOCS1
CD38, SOCS3, CDKN1A, GADD45B, and B4GALT5
CD38, SOCS3, CDKN1A, GADD45B, and IL15RA
CD38, SOCS3, CDKN1A, GADD45B, and TNFAIP3
CD38, SOCS3, CDKN1A, GADD45B, and SOCS1
CD38, SOCS3, CDKN1A, B4GALT5, and IL15RA
CD38, SOCS3, CDKN1A, B4GALT5, and TNFAIP3
CD38, SOCS3, CDKN1A, B4GALT5, and SOCS1
CD38, SOCS3, CDKN1A, IL15RA, and TNFAIP3
CD38, SOCS3, CDKN1A, IL15RA, and SOCS1
CD38, SOCS3, CDKN1A, TNFAIP3, and SOCS1
CD38, SOCS3, GADD45B, B4GALT5, and IL15RA
CD38, SOCS3, GADD45B, B4GALT5, and TNFAIP3
CD38, SOCS3, GADD45B, B4GALT5, and SOCS1
CD38, SOCS3, GADD45B, IL15RA, and TNFAIP3
CD38, SOCS3, GADD45B, IL15RA, and SOCS1
CD38, SOCS3, GADD45B, TNFAIP3, and SOCS1
CD38, SOCS3, B4GALT5, IL15RA, and TNFAIP3
CD38, SOCS3, B4GALT5, IL15RA, and SOCS1
CD38, SOCS3, B4GALT5, TNFAIP3, and SOCS1
CD38, SOCS3, IL15RA, TNFAIP3, and SOCS1
CD38, AQP9, CDKN1A, GADD45B, and B4GALT5
CD38, AQP9, CDKN1A, GADD45B, and IL15RA
CD38, AQP9, CDKN1A, GADD45B, and TNFAIP3
CD38, AQP9, CDKN1A, GADD45B, and SOCS1
CD38, AQP9, CDKN1A, B4GALT5, and IL15RA
CD38, AQP9, CDKN1A, B4GALT5, and TNFAIP3

CD38, AQP9, CDKN1A, B4GALT5, and SOCS1
CD38, AQP9, CDKN1A, IL15RA, and TNFAIP3
CD38, AQP9, CDKN1A, IL15RA, and SOCS1
CD38, AQP9, CDKN1A, TNFAIP3, and SOCS1
CD38, AQP9, GADD45B, B4GALT5, and IL15RA
CD38, AQP9, GADD45B, B4GALT5, and TNFAIP3
CD38, AQP9, GADD45B, B4GALT5, and SOCS1
CD38, AQP9, GADD45B, IL15RA, and TNFAIP3
CD38, AQP9, GADD45B, IL15RA, and SOCS1
CD38, AQP9, GADD45B, TNFAIP3, and SOCS1
CD38, AQP9, B4GALT5, IL15RA, and TNFAIP3
CD38, AQP9, B4GALT5, IL15RA, and SOCS1
CD38, AQP9, B4GALT5, TNFAIP3, and SOCS1
CD38, AQP9, IL15RA, TNFAIP3, and SOCS1
CD38, CDKN1A, GADD45B, B4GALT5, and IL15RA
CD38, CDKN1A, GADD45B, B4GALT5, and TNFAIP3
CD38, CDKN1A, GADD45B, B4GALT5, and SOCS1
CD38, CDKN1A, GADD45B, IL15RA, and TNFAIP3
CD38, CDKN1A, GADD45B, IL15RA, and SOCS1
CD38, CDKN1A, GADD45B, TNFAIP3, and SOCS1
CD38, CDKN1A, B4GALT5, IL15RA, and TNFAIP3
CD38, CDKN1A, B4GALT5, IL15RA, and SOCS1
CD38, CDKN1A, B4GALT5, TNFAIP3, and SOCS1
CD38, CDKN1A, IL15RA, TNFAIP3, and SOCS1
CD38, GADD45B, B4GALT5, IL15RA, and TNFAIP3
CD38, GADD45B, B4GALT5, IL15RA, and SOCS1
CD38, GADD45B, B4GALT5, TNFAIP3, and SOCS1
CD38, GADD45B, IL15RA, TNFAIP3, and SOCS1
CD38, B4GALT5, IL15RA, TNFAIP3, and SOCS1
SOCS3, AQP9, CDKN1A, GADD45B, and B4GALT5
SOCS3, AQP9, CDKN1A, GADD45B, and IL15RA
SOCS3, AQP9, CDKN1A, GADD45B, and TNFAIP3
SOCS3, AQP9, CDKN1A, GADD45B, and SOCS1
SOCS3, AQP9, CDKN1A, B4GALT5, and IL15RA
SOCS3, AQP9, CDKN1A, B4GALT5, and TNFAIP3
SOCS3, AQP9, CDKN1A, B4GALT5, and SOCS1
SOCS3, AQP9, CDKN1A, IL15RA, and TNFAIP3
SOCS3, AQP9, CDKN1A, IL15RA, and SOCS1
SOCS3, AQP9, CDKN1A, TNFAIP3, and SOCS1
SOCS3, AQP9, GADD45B, B4GALT5, and IL15RA
SOCS3, AQP9, GADD45B, B4GALT5, and TNFAIP3
SOCS3, AQP9, GADD45B, B4GALT5, and SOCS1
SOCS3, AQP9, GADD45B, IL15RA, and TNFAIP3
SOCS3, AQP9, GADD45B, IL15RA, and SOCS1
SOCS3, AQP9, GADD45B, TNFAIP3, and SOCS1
SOCS3, AQP9, B4GALT5, IL15RA, and TNFAIP3
SOCS3, AQP9, B4GALT5, IL15RA, and SOCS1
SOCS3, AQP9, B4GALT5, TNFAIP3, and SOCS1
SOCS3, AQP9, IL15RA, TNFAIP3, and SOCS1
SOCS3, CDKN1A, GADD45B, B4GALT5, and IL15RA
SOCS3, CDKN1A, GADD45B, B4GALT5, and TNFAIP3
SOCS3, CDKN1A, GADD45B, B4GALT5, and SOCS1

SOCS3, CDKN1A, GADD45B, IL15RA, and TNFAIP3
SOCS3, CDKN1A, GADD45B, IL15RA, and SOCS1
SOCS3, CDKN1A, GADD45B, TNFAIP3, and SOCS1
SOCS3, CDKN1A, B4GALT5, IL15RA, and TNFAIP3
SOCS3, CDKN1A, B4GALT5, IL15RA, and SOCS1
SOCS3, CDKN1A, B4GALT5, TNFAIP3, and SOCS1
SOCS3, CDKN1A, IL15RA, TNFAIP3, and SOCS1
SOCS3, GADD45B, B4GALT5, IL15RA, and TNFAIP3
SOCS3, GADD45B, B4GALT5, IL15RA, and SOCS1
SOCS3, GADD45B, B4GALT5, TNFAIP3, and SOCS1
SOCS3, GADD45B, IL15RA, TNFAIP3, and SOCS1
SOCS3, B4GALT5, IL15RA, TNFAIP3, and SOCS1
AQP9, CDKN1A, GADD45B, B4GALT5, and IL15RA
AQP9, CDKN1A, GADD45B, B4GALT5, and TNFAIP3
AQP9, CDKN1A, GADD45B, B4GALT5, and SOCS1
AQP9, CDKN1A, GADD45B, IL15RA, and TNFAIP3
AQP9, CDKN1A, GADD45B, IL15RA, and SOCS1
AQP9, CDKN1A, GADD45B, TNFAIP3, and SOCS1
AQP9, CDKN1A, B4GALT5, IL15RA, and TNFAIP3
AQP9, CDKN1A, B4GALT5, IL15RA, and SOCS1
AQP9, CDKN1A, B4GALT5, TNFAIP3, and SOCS1
AQP9, CDKN1A, IL15RA, TNFAIP3, and SOCS1
AQP9, GADD45B, B4GALT5, IL15RA, and TNFAIP3
AQP9, GADD45B, B4GALT5, IL15RA, and SOCS1
AQP9, GADD45B, B4GALT5, TNFAIP3, and SOCS1
AQP9, GADD45B, IL15RA, TNFAIP3, and SOCS1
AQP9, B4GALT5, IL15RA, TNFAIP3, and SOCS1
CDKN1A, GADD45B, B4GALT5, IL15RA, and TNFAIP3
CDKN1A, GADD45B, B4GALT5, IL15RA, and SOCS1
CDKN1A, GADD45B, B4GALT5, TNFAIP3, and SOCS1
CDKN1A, GADD45B, IL15RA, TNFAIP3, and SOCS1
CDKN1A, B4GALT5, IL15RA, TNFAIP3, and SOCS1
GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1

In some embodiments of the diagnostic methods described herein, the expression levels of a combination of six genes set forth in Table 1, such as any of the exemplary combinations shown in Table 6, may be determined.

5

Table 6. Exemplary Six-Gene Combinations of IRAK4 Biomarkers

CD38, SOCS3, AQP9, CDKN1A, GADD45B, and B4GALT5
CD38, SOCS3, AQP9, CDKN1A, GADD45B, and IL15RA
CD38, SOCS3, AQP9, CDKN1A, GADD45B, and TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, GADD45B, and SOCS1
CD38, SOCS3, AQP9, CDKN1A, B4GALT5, and IL15RA
CD38, SOCS3, AQP9, CDKN1A, B4GALT5, and TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, B4GALT5, and SOCS1
CD38, SOCS3, AQP9, CDKN1A, IL15RA, and TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, IL15RA, and SOCS1
CD38, SOCS3, AQP9, CDKN1A, TNFAIP3, and SOCS1
CD38, SOCS3, AQP9, GADD45B, B4GALT5, and IL15RA

CD38, SOCS3, AQP9, GADD45B, B4GALT5, and TNFAIP3
CD38, SOCS3, AQP9, GADD45B, B4GALT5, and SOCS1
CD38, SOCS3, AQP9, GADD45B, IL15RA, and TNFAIP3
CD38, SOCS3, AQP9, GADD45B, IL15RA, and SOCS1
CD38, SOCS3, AQP9, GADD45B, TNFAIP3, and SOCS1
CD38, SOCS3, AQP9, B4GALT5, IL15RA, and TNFAIP3
CD38, SOCS3, AQP9, B4GALT5, IL15RA, and SOCS1
CD38, SOCS3, AQP9, B4GALT5, TNFAIP3, and SOCS1
CD38, SOCS3, AQP9, IL15RA, TNFAIP3, and SOCS1
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5, and IL15RA
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5, and TNFAIP3
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5, and SOCS1
CD38, SOCS3, CDKN1A, GADD45B, IL15RA, and TNFAIP3
CD38, SOCS3, CDKN1A, GADD45B, IL15RA, and SOCS1
CD38, SOCS3, CDKN1A, GADD45B, TNFAIP3, and SOCS1
CD38, SOCS3, CDKN1A, B4GALT5, IL15RA, and TNFAIP3
CD38, SOCS3, CDKN1A, B4GALT5, IL15RA, and SOCS1
CD38, SOCS3, CDKN1A, B4GALT5, TNFAIP3, and SOCS1
CD38, SOCS3, CDKN1A, IL15RA, TNFAIP3, and SOCS1
CD38, SOCS3, GADD45B, B4GALT5, IL15RA, and TNFAIP3
CD38, SOCS3, GADD45B, B4GALT5, IL15RA, and SOCS1
CD38, SOCS3, GADD45B, B4GALT5, TNFAIP3, and SOCS1
CD38, SOCS3, GADD45B, IL15RA, TNFAIP3, and SOCS1
CD38, SOCS3, B4GALT5, IL15RA, TNFAIP3, and SOCS1
CD38, AQP9, CDKN1A, GADD45B, B4GALT5, and IL15RA
CD38, AQP9, CDKN1A, GADD45B, B4GALT5, and TNFAIP3
CD38, AQP9, CDKN1A, GADD45B, B4GALT5, and SOCS1
CD38, AQP9, CDKN1A, GADD45B, IL15RA, and TNFAIP3
CD38, AQP9, CDKN1A, GADD45B, IL15RA, and SOCS1
CD38, AQP9, CDKN1A, GADD45B, TNFAIP3, and SOCS1
CD38, AQP9, CDKN1A, B4GALT5, IL15RA, and TNFAIP3
CD38, AQP9, CDKN1A, B4GALT5, IL15RA, and SOCS1
CD38, AQP9, CDKN1A, B4GALT5, TNFAIP3, and SOCS1
CD38, AQP9, CDKN1A, IL15RA, TNFAIP3, and SOCS1
CD38, AQP9, GADD45B, B4GALT5, IL15RA, and TNFAIP3
CD38, AQP9, GADD45B, B4GALT5, IL15RA, and SOCS1
CD38, AQP9, GADD45B, B4GALT5, TNFAIP3, and SOCS1
CD38, AQP9, GADD45B, IL15RA, TNFAIP3, and SOCS1
CD38, AQP9, B4GALT5, IL15RA, TNFAIP3, and SOCS1
CD38, CDKN1A, GADD45B, B4GALT5, IL15RA, and TNFAIP3
CD38, CDKN1A, GADD45B, B4GALT5, IL15RA, and SOCS1
CD38, CDKN1A, GADD45B, B4GALT5, TNFAIP3, and SOCS1
CD38, CDKN1A, GADD45B, IL15RA, TNFAIP3, and SOCS1
CD38, CDKN1A, B4GALT5, IL15RA, TNFAIP3, and SOCS1
CD38, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, and IL15RA
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, and TNFAIP3
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, and SOCS1
SOCS3, AQP9, CDKN1A, GADD45B, IL15RA, and TNFAIP3
SOCS3, AQP9, CDKN1A, GADD45B, IL15RA, and SOCS1
SOCS3, AQP9, CDKN1A, GADD45B TNFAIP3, and SOCS1
SOCS3, AQP9, CDKN1A, B4GALT5, IL15RA, and TNFAIP3

SOCS3, AQP9, CDKN1A, B4GALT5, IL15RA, and SOCS1
SOCS3, AQP9, CDKN1A, B4GALT5, TNFAIP3, and SOCS1
SOCS3, AQP9, CDKN1A, IL15RA, TNFAIP3, and SOCS1
SOCS3, AQP9, GADD45B, B4GALT5, IL15RA, and TNFAIP3
SOCS3, AQP9, GADD45B, B4GALT5, IL15RA, and SOCS1
SOCS3, AQP9, GADD45B, B4GALT5, TNFAIP3, and SOCS1
SOCS3, AQP9, GADD45B, IL15RA, TNFAIP3, and SOCS1
SOCS3, AQP9, B4GALT5, IL15RA, TNFAIP3, and SOCS1
SOCS3, CDKN1A, GADD45B, B4GALT5, IL15RA, and TNFAIP3
SOCS3, CDKN1A, GADD45B, B4GALT5, IL15RA, and SOCS1
SOCS3, CDKN1A, GADD45B, B4GALT5, TNFAIP3, and SOCS1
SOCS3, CDKN1A, GADD45B, IL15RA, TNFAIP3, and SOCS1
SOCS3, CDKN1A, B4GALT5, IL15RA, TNFAIP3, and SOCS1
SOCS3, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1
AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, and TNFAIP3
AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, and SOCS1
AQP9, CDKN1A, GADD45B, B4GALT5, TNFAIP3, and SOCS1
AQP9, CDKN1A, GADD45B, IL15RA, TNFAIP3, and SOCS1
AQP9, CDKN1A, B4GALT5, IL15RA, TNFAIP3, and SOCS1
AQP9, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1
CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1

In some embodiments of the diagnostic methods described herein, the expression levels of a combination of seven genes set forth in Table 1, such as any of the exemplary combinations shown in Table 7, may be determined.

Table 7. Exemplary Seven-Gene Combinations of IRAK4 Biomarkers

CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, and IL15RA
CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, and TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, and SOCS1
CD38, SOCS3, AQP9, CDKN1A, GADD45B, IL15RA, and TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, GADD45B, IL15RA, and SOCS1
CD38, SOCS3, AQP9, CDKN1A, GADD45B, TNFAIP3, and SOCS1
CD38, SOCS3, AQP9, CDKN1A, B4GALT5, IL15RA, and TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, B4GALT5, IL15RA, and SOCS1
CD38, SOCS3, AQP9, CDKN1A, B4GALT5, TNFAIP3, and SOCS1
CD38, SOCS3, AQP9, CDKN1A, IL15RA, TNFAIP3, and SOCS1
CD38, SOCS3, AQP9, GADD45B, B4GALT5, IL15RA, and TNFAIP3
CD38, SOCS3, AQP9, GADD45B, B4GALT5, IL15RA, and SOCS1
CD38, SOCS3, AQP9, GADD45B, B4GALT5, TNFAIP3, and SOCS1
CD38, SOCS3, AQP9, GADD45B, IL15RA, TNFAIP3, and SOCS1
CD38, SOCS3, AQP9, B4GALT5, IL15RA, TNFAIP3, and SOCS1
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5, IL15RA, and TNFAIP3
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5, IL15RA, and SOCS1
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5, TNFAIP3, and SOCS1
CD38, SOCS3, CDKN1A, GADD45B, IL15RA, TNFAIP3, and SOCS1
CD38, SOCS3, CDKN1A, B4GALT5, IL15RA, TNFAIP3, and SOCS1
CD38, SOCS3, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1
CD38, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, and TNFAIP3
CD38, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, and SOCS1

CD38, AQP9, CDKN1A, GADD45B, B4GALT5, TNFAIP3, and SOCS1
CD38, AQP9, CDKN1A, GADD45B, IL15RA, TNFAIP3, and SOCS1
CD38, AQP9, CDKN1A, B4GALT5, IL15RA, TNFAIP3, and SOCS1
CD38, AQP9, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1
CD38, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, and TNFAIP3
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, and SOCS1
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, TNFAIP3, and SOCS1
SOCS3, AQP9, CDKN1A, GADD45B, IL15RA, TNFAIP3, and SOCS1
SOCS3, AQP9, CDKN1A, B4GALT5, IL15RA, TNFAIP3, and SOCS1
SOCS3, AQP9, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1
SOCS3, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1
AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1

In some embodiments of the diagnostic methods described herein, the expression levels of a combination of eight genes set forth in Table 1, such as any of the exemplary combinations shown in Table 8, may be determined.

Table 8. Exemplary Eight-Gene Combinations of IRAK4 Biomarkers

CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, and TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, and SOCS1
CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, TNFAIP3, and SOCS1
CD38, SOCS3, AQP9, CDKN1A, GADD45B, IL15RA, TNFAIP3, and SOCS1
CD38, SOCS3, AQP9, CDKN1A, B4GALT5, IL15RA, TNFAIP3, and SOCS1
CD38, SOCS3, AQP9, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1
CD38, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1

The presence and/or expression level (amount) of the IRAK4 pathway biomarkers described herein in a sample can be analyzed by a number of methodologies, many of which are known in the art and understood by the skilled artisan, including, but not limited to, immunohistochemistry ("IHC"), Western blot analysis, immunoprecipitation, molecular binding assays, enzyme-linked immunosorbent assay (ELISA), enzyme-linked immunofiltration assay (ELIFA), fluorescence activated cell sorting ("FACS"), MassARRAY, proteomics, quantitative blood based assays (e.g., serum ELISA), biochemical enzymatic activity assays, in situ hybridization, fluorescence in situ hybridization (FISH), Southern analysis, Northern analysis, whole genome sequencing, polymerase chain reaction (PCR) (including quantitative PCR (qPCR)) and other amplification type detection methods, such as, for example, branched DNA, SISBA, TMA and the like), RNA-Seq, microarray analysis, gene expression profiling, and/or serial analysis of gene expression ("SAGE"), as well as any one of the wide variety of assays that can be performed by protein, gene, and/or tissue array analysis. Typical protocols for evaluating the status of genes and gene products are found, for example in Ausubel et al., eds., 1995, *Current Protocols In Molecular Biology*, Units 2 (Northern Blotting), 4 (Southern Blotting), 15 (Immunoblotting) and 18 (PCR Analysis). Multiplexed immunoassays such as those available from Rules Based Medicine or Meso Scale Discovery ("MSD") may also be used.

In any of the preceding methods, the presence and/or expression level (amount) of a biomarker (e.g., CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, BCL2A1, CXCL10, CCL8, GPR84, C15orf48, DRAM1, CXCL11, TNFAIP6, CSRNP1, PLSCR1, CLEC4E, SAMSN1, and/or ACSL1) may be a nucleic acid expression level. In some instances, the nucleic acid expression level is determined using qPCR, RT-PCR, RNA-Seq, multiplex qPCR or RT-qPCR, microarray analysis, SAGE, MassARRAY technique, or *in situ* hybridization (e.g., FISH).

In a particular instance, the expression level of a biomarker (e.g., CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, BCL2A1, CXCL10, CCL8, GPR84, C15orf48, DRAM1, CXCL11, TNFAIP6, CSRNP1, PLSCR1, CLEC4E, SAMSN1, and/or ACSL1) is an mRNA expression level. Methods for the evaluation of mRNAs in cells are well known and include, for example, qPCR, RNA-Seq (e.g., whole transcriptome shotgun sequencing) using next generation sequencing techniques, hybridization assays using complementary DNA probes (such as in situ hybridization using labeled riboprobes specific for the one or more genes, Northern blot and related techniques) and various nucleic acid amplification assays (such as RT-PCR using complementary primers specific for one or more of the genes, and other amplification type detection methods, such as, for example, branched DNA, SISBA, TMA and the like). In addition, such methods can include one or more steps that allow one to determine the levels of target mRNA in a biological sample (e.g., by simultaneously examining the levels a comparative control mRNA sequence of a “housekeeping” gene such as an actin family member). Optionally, the sequence of the amplified target cDNA can be determined. Optional methods include protocols that examine or detect mRNAs, such as target mRNAs, in a tissue or cell sample by microarray technologies. Using nucleic acid microarrays test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. For example, a selection of genes whose expression correlates with increased or reduced clinical benefit of treatment including an IRAK4 pathway inhibitor may be arrayed on a solid support. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene.

In any of the preceding methods, the presence and/or expression level (amount) of a biomarker (e.g., CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, BCL2A1, CXCL10, CCL8, GPR84, C15orf48, DRAM1, CXCL11, TNFAIP6, CSRNP1, PLSCR1, CLEC4E, SAMSN1, and/or ACSL1) is measured by determining protein expression levels of the biomarker. In certain instances, the method comprises contacting the biological sample with antibodies that specifically bind to a biomarker described herein under conditions permissive for binding of the biomarker, and detecting whether a complex is formed between the antibodies and biomarker. Such method may be an *in vitro* or *in vivo* method. Any method of measuring protein expression levels known in the art may be used. For example, in some instances, a protein expression level of a biomarker (e.g., CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, BCL2A1, CXCL10, CCL8, GPR84, C15orf48, DRAM1, CXCL11, TNFAIP6, CSRNP1, PLSCR1, CLEC4E, SAMSN1, and/or ACSL1) is determined using a method selected from the group consisting of flow

cytometry (e.g., fluorescence-activated cell sorting (FACS™)), Western blot, ELISA, ELIFA, immunoprecipitation, immunohistochemistry (IHC), immunofluorescence, radioimmunoassay, dot blotting, immunodetection methods, HPLC, surface plasmon resonance, optical spectroscopy, mass spectrometry, and HPLC.

In certain instances, a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is a single sample or a combination of multiple samples from the same subject or individual that are obtained at one or more different time points than when the test sample is obtained. For example, a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained at an earlier time point from the same subject or individual than when the test sample is obtained. Such reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue may be useful if the reference sample is obtained during initial diagnosis of an IRAK4-mediated disorder or condition and the test sample is later obtained when the IRAK4-mediated disorder or condition becomes more severe.

In certain embodiments, a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is a combination of multiple samples from one or more healthy individuals who are not the patient. In certain embodiments, a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is a combination of multiple samples from one or more individuals with a disease or disorder (e.g., an IRAK4-mediated disorder or condition) who are not the patient or individual. In certain embodiments, a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is pooled RNA samples from normal tissues or pooled plasma or serum samples from one or more individuals who are not the patient. In certain embodiments, a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is pooled RNA samples from pooled plasma or serum samples from one or more individuals with an IRAK4-mediated disorder or condition (e.g., an inflammatory disorder or an immune disorder) who are not the patient. In certain embodiments, the reference level is the median level of expression of a biomarker across a set of samples. In certain embodiments, the reference level is the median level of expression of a biomarker across a population of patients having a particular disease or disorder (e.g., an IRAK4-mediated disorder or condition (e.g., an inflammatory disorder or an immune disorder)).

In any of the preceding diagnostic methods, the IRAK4-mediated disorder or condition is selected from the group consisting of an immune disorder, an inflammatory disorder, a fibrotic disorder, an eosinophilic disorder, an infection, pain, a central nervous system disorder, an acute kidney injury, a chronic kidney disease, endometriosis, non-alcoholic fatty liver disease, a metabolic syndrome, and obesity.

In some instances, the immune disorder is allergic airway syndrome, allergic rhinitis, allograft rejection, asthma, atopic dermatitis, contact dermatitis, Crohn's disease, cutaneous lupus, delayed hypersensitivity, diabetes, gout, graft versus host disease, graft rejection, inflammatory bowel disease (IBD), inflammatory myositis (e.g., polymyositis, dermatomyositis), lupus, lupus nephritis, multiple sclerosis, psoriasis, rheumatoid arthritis, scleroderma, sepsis, systemic lupus erythematosus, systemic sclerosis, or ulcerative colitis.

In some instances, the inflammatory disorder is acute respiratory distress syndrome, acute lung injury, adult onset Still's disease, allergic airway syndrome, allergic rhinitis, asthma, atherosclerosis, atopic dermatitis, bronchitis, calcium pyrophosphate deposition disease (CPPD), cerebrovascular accident (e.g., stroke), chronic obstructive pulmonary disease (COPD), contact dermatitis, Crohn's disease, cryopyrin-associated periodic syndromes (CAPS), cutaneous lupus, delayed hypersensitivity, gout, graft versus host disease, inflammatory bowel disease (IBD), inflammatory myositis (e.g., polymyositis, dermatomyositis), lupus, lupus nephritis, rheumatoid arthritis, rhinitis, scleroderma, sepsis, systemic lupus erythematosus, systemic onset juvenile idiopathic arthritis, systemic sclerosis, or ulcerative colitis.

In some instances, the eosinophilic disorder is allergic rhinitis, asthma, atopic dermatitis, chronic obstructive pulmonary disease (COPD), or contact dermatitis.

In some instances, the fibrotic disorder is atherosclerosis, scleroderma, or systemic sclerosis.

In some instances, the central nervous system disorder is cerebrovascular accident (e.g., stroke), multiple sclerosis, or neurodegeneration.

In some instances, the pain is neuropathic pain.

In some instances, the infection is bronchitis or sepsis.

In any of the preceding diagnostic methods of the invention, the IRAK4 pathway inhibitor is an IRAK4 inhibitor, an IRAK1 inhibitor, a toll-like receptor (TLR) inhibitor, an interleukin-1 receptor (IL-1R) inhibitor, an interleukin-33 receptor (IL-33R) inhibitor, or a myeloid differentiation primary response gene 88 (MyD88) inhibitor. In one instance, the IRAK4 pathway inhibitor is an IRAK4 inhibitor. In some instances, the IRAK4 pathway inhibitor is a TLR inhibitor. In some instances, the TLR inhibitor is a TLR7 inhibitor, a TLR8 inhibitor, a TLR9 inhibitor, a TLR1 inhibitor, a TLR2 inhibitor, a TLR4 inhibitor, a TLR5 inhibitor, a TLR6 inhibitor, or a TLR10 inhibitor. In certain instances, the IRAK4 pathway inhibitor is a TLR7 inhibitor, a TLR8 inhibitor, or both a TLR7 and TLR8 inhibitor. In certain instances, the IRAK4 pathway inhibitor is a TLR9 inhibitor. In any one of the preceding embodiments, the IRAK4 pathway inhibitor is a small molecule inhibitor. In other embodiments, the IRAK4 pathway inhibitor is a protein or multi-protein complex, such as an antibody.

B. Methods of Treatment with IRAK4 Pathway Inhibitors

The present invention also provides methods for treating a patient having IRAK4-mediated disorders or conditions (e.g., immune disorders (e.g., systemic lupus erythematosus (SLE)) or inflammatory disorders (e.g., asthma)). Accordingly, in some instances, the methods of the invention include administering to the patient an IRAK4 pathway inhibitor. Any of the IRAK4 pathway inhibitors described above or known in the art may be used in connection with the methods.

In one aspect, the invention features a method of treating a patient having an IRAK4-mediated disorder or condition with an IRAK4 pathway inhibitor, the method (a) determining, in a sample obtained from the patient at a time point following administration of a first dose of the IRAK4 pathway inhibitor, the expression level of one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1; (b) comparing the expression level of the one or more genes set forth in Table 1 in the sample with a reference expression level; and (c) administering at least a

second dose of the IRAK4 pathway inhibitor to the patient based on a decreased expression level of the one or more genes set forth in Table 1 relative to the reference expression level.

In some instances, the expression level of the one or more genes set forth in Table 1 is decreased in the sample obtained from the patient at a time point following administration of a first dose of the IRAK4 pathway inhibitor relative to the reference expression level. For example, in some instances, the expression level of the one or more genes set forth in Table 1 is decreased by about 1% or more (e.g., about 2% or more, about 3% or more, about 4% or more, about 5% or more, about 6% or more, about 7% or more, about 8% or more, about 9% or more, about 10% or more, about 11% or more, about 12% or more, about 13% or more, about 14% or more, about 15% or more, about 20% or more, about 25% or more, about 30% or more, about 35% or more, about 40% or more, about 45% or more, about 50% or more, about 55% or more, about 60% or more, about 65% or more, about 70% or more, about 75% or more, about 80% or more, about 85% or more, about 90% or more, about 95% or more, or about 100%), e.g., from about 1% to about 5%, from about 5% to about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 35%, from about 35% to about 40%, from about 40% to about 45%, from about 45% to about 50%, from about 50% to about 55%, from about 55% to about 60%, from about 60% to about 65%, from about 65% to about 70%, from about 70% to about 75%, from about 75% to about 80%, from about 80% to about 85%, from about 85% to about 90%, from about 90% to about 95%, or from about 95% to about 100%, relative to a reference expression level (e.g., the expression level of the one or more genes set forth in Table 1 in a sample from the patient obtained prior to administration of the first dose of the IRAK4 pathway inhibitor). In other instances, the expression level of the one or more genes set forth in Table 1 is decreased by about 0.5-fold, about 0.6-fold, about 0.7-fold, about 0.8-fold, about 0.9-fold, about 1-fold, about 1.1-fold, about 1.2-fold, about 1.3-fold, about 1.4-fold, about 1.5-fold, about 1.6-fold, about 1.7-fold, about 1.8-fold, about 1.9-fold, about 2-fold, about 2.1-fold, about 2.2-fold, about 2.3-fold, about 2.4-fold, about 2.5-fold, about 3-fold, about 3.5-fold, about 4-fold, about 4.5-fold, about 5-fold, about 5.5-fold, about 6-fold, about 6.5-fold, about 7-fold, about 7.5-fold, about 8-fold, about 8.5-fold, about 9-fold, about 9.5-fold, or about 10-fold or greater, e.g., from about 0.5-fold to about 0.7-fold, from about 0.7-fold to about 1-fold, from about 1-fold to about 1.5-fold, from about 1.5-fold to about 2-fold, from about 2-fold to about 3-fold, from about 3-fold to about 4-fold, from about 4-fold to about 5-fold, from about 5-fold to about 6-fold, from about 6-fold to about 7-fold, from about 7-fold to about 8-fold, or from about 9-fold to about 10-fold or greater, relative to the reference expression level (e.g., the expression level of the one or more genes set forth in Table 1 in a sample from the patient obtained prior to administration of the first dose of the IRAK4 pathway inhibitor).

In some embodiments, reduced or decreased expression refers to an overall reduction of about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or greater, in the level of biomarker (e.g., protein or nucleic acid (e.g., gene or mRNA)), detected by standard art known methods such as those described herein, as compared to a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. In certain embodiments, reduced expression refers to the decrease in expression level (amount) of a biomarker in the sample wherein the decrease is at least about any of 0.9x, 0.8x, 0.7x, 0.6x, 0.5x, 0.4x, 0.3x, 0.2x, 0.1x, 0.05x, or 0.01x the

expression level (amount) of the respective biomarker in a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue.

In certain instances, the method includes administering to a patient having an IRAK4-mediated disorder or condition who has already received a first dose of an IRAK4 pathway inhibitor, at least a second dose of the IRAK4 pathway inhibitor based on a decreased expression level of the one or more genes set forth in Table 1 relative to the reference expression level. In some instances, the method includes administering to a patient having an IRAK4-mediated disorder or condition who has already received a first dose of an IRAK4 pathway inhibitor, at least a second dose of the IRAK4 pathway inhibitor based on a decreased expression level of one or more genes (e.g., one gene, two genes, three genes, four genes, five genes, six genes, seven genes, eight genes, nine genes, ten genes, eleven genes, or all twelve genes) selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1 relative to a reference expression level. In some instances, the method includes administering to a patient having an IRAK4-mediated disorder or condition who has already received a first dose of an IRAK4 pathway inhibitor, at least a second dose of the IRAK4 pathway inhibitor based on a decreased expression level of one or more genes (e.g., one gene, two genes, three genes, four genes, five genes, six genes, seven genes, eight genes, nine genes, ten genes, or all eleven genes) selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3 relative to a reference expression level. In other instances, the method includes administering to a patient having an IRAK4-mediated disorder or condition who has already received a first dose of an IRAK4 pathway inhibitor, at least a second dose of the IRAK4 pathway inhibitor based on a decreased expression level of one or more genes (e.g., one gene, two genes, three genes, four genes, five genes, six genes, seven genes, eight genes, or all nine genes) selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1 relative to a reference expression level.

In any one the preceding embodiments, the reference expression level can be: (i) the expression level of the one or more genes set forth in Table 1 in a sample from the patient obtained prior to administration of the first dose of the IRAK4 pathway inhibitor; (ii) the expression level of the one or more genes set forth in Table 1 in a reference population (e.g., a median expression level of the one or more genes set forth in Table 1 in a reference population); (iii) a pre-assigned expression level for the one or more genes set forth in Table 1; (iv) the expression level of the one or more genes set forth in Table 1 in a sample obtained from the patient at a previous time point, wherein the previous time point is following administration of the first dose of the IRAK4 pathway inhibitor; or (v) the expression level of the one or more genes set forth in Table 1 in a sample obtained from the patient at a subsequent time point.

In another aspect, the invention features a therapeutic method of treating a patient having an IRAK4-mediated disorder or condition, the method comprising administering to the patient an IRAK4 pathway inhibitor, wherein prior to treatment the expression level of one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 in a sample obtained from the patient has been determined to be increased relative to a reference expression level.

In some instances, the expression level of one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 has been determined to be increased in the sample obtained from the patient relative to the reference expression level. For example, in some instances, the expression level of the one or more genes set forth in Table 1 has been determined to be increased by about 1% or more (e.g., about 2% or more, about 3% or more, about 4% or more, about 5% or more, about 6% or more, about 7% or more, about 8% or more, about 9% or more, about 10% or more, about 11% or more, about 12% or more, about 13% or more, about 14% or more, about 15% or more, about 20% or more, about 25% or more, about 30% or more, about 35% or more, about 40% or more, about 45% or more, about 50% or more, about 55% or more, about 60% or more, about 65% or more, about 70% or more, about 75% or more, about 80% or more, about 85% or more, about 90% or more, about 95% or more, or about 100%), e.g., from about 1% to about 5%, from about 5% to about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 35%, from about 35% to about 40%, from about 40% to about 45%, from about 45% to about 50%, from about 50% to about 55%, from about 55% to about 60%, from about 60% to about 65%, from about 65% to about 70%, from about 70% to about 75%, from about 75% to about 80%, from about 80% to about 85%, from about 85% to about 90%, from about 90% to about 95%, or from about 95% to about 100%, relative to a reference expression level (e.g., the expression level of the one or more genes set forth in Table 1 in a reference population, e.g., a median expression level of the one or more genes set forth in Table 1 in a reference population). In other instances, the expression level of the one or more genes set forth in Table 1 has been determined to be increased by about 0.5-fold, about 0.6-fold, about 0.7-fold, about 0.8-fold, about 0.9-fold, about 1-fold, about 1.1-fold, about 1.2-fold, about 1.3-fold, about 1.4-fold, about 1.5-fold, about 1.6-fold, about 1.7-fold, about 1.8-fold, about 1.9-fold, about 2-fold, about 2.1-fold, about 2.2-fold, about 2.3-fold, about 2.4-fold, about 2.5-fold, about 3-fold, about 3.5-fold, about 4-fold, about 4.5-fold, about 5-fold, about 5.5-fold, about 6-fold, about 6.5-fold, about 7-fold, about 7.5-fold, about 8-fold, about 8.5-fold, about 9-fold, about 9.5-fold, or about 10-fold or greater, e.g., from about 0.5-fold to about 0.7-fold, from about 0.7-fold to about 1-fold, from about 1-fold to about 1.5-fold, from about 1.5-fold to about 2-fold, from about 2-fold to about 3-fold, from about 3-fold to about 4-fold, from about 4-fold to about 5-fold, from about 5-fold to about 6-fold, from about 6-fold to about 7-fold, from about 7-fold to about 8-fold, or from about 9-fold to about 10-fold or greater, relative to the reference expression level (e.g., e.g., the expression level of the one or more genes set forth in Table 1 in a reference population, e.g., a median expression level of the one or more genes set forth in Table 1 in a reference population). In some embodiments, elevated or increased expression refers to an overall increase of about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or greater, in the level of biomarker (e.g., protein or nucleic acid (e.g., gene or mRNA)), detected by standard art-known methods such as those described herein, as compared to a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue.

In certain embodiments, the elevated or increased expression refers to the increase in expression level (amount) of a biomarker in the sample, wherein the increase is at least about any of 1.5x, 1.75x, 2x, 3x, 4x, 5x, 6x, 7x, 8x, 9x, 10x, 25x, 50x, 75x, or 100x the expression level (amount) of the respective

biomarker in a reference level, reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. In some embodiments, elevated expression refers to an overall increase of greater than about 1.5-fold, about 1.75-fold, about 2-fold, about 2.25-fold, about 2.5-fold, about 2.75-fold, about 3.0-fold, or about 3.25-fold as compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (e.g., housekeeping gene).

In certain embodiments, the method includes administering to a patient an IRAK4 pathway inhibitor when an increased expression level of one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 relative to a reference expression level identifies the patient as having an increased likelihood of benefit from treatment with an IRAK4 pathway inhibitor.

In certain instances, the method includes administering to a patient having an IRAK4-mediated disorder or condition an IRAK4 pathway inhibitor when an increased level of expression of one or more genes (e.g., one gene, two genes, three genes, four genes, five genes, six genes, seven genes, eight genes, nine genes, ten genes, eleven genes, or all twelve genes) selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1, relative to a reference expression level, identifies the patient as having an increased likelihood of benefit from treatment with an IRAK4 pathway inhibitor. In some instances, the method includes administering to a patient having an IRAK4-mediated disorder or condition an IRAK4 pathway inhibitor when an increased level of expression of one or more genes (e.g., one gene, two genes, three genes, four genes, five genes, six genes, seven genes, eight genes, nine genes, ten genes, or all eleven genes) selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3, relative to a reference expression level, identifies the patient as having an increased likelihood of benefit from treatment with an IRAK4 pathway inhibitor. In some instances, the method includes administering to a patient having an IRAK4-mediated disorder or condition an IRAK4 pathway inhibitor when an increased level of expression of one or more genes (e.g., one gene, two genes, three genes, four genes, five genes, six genes, seven genes, eight genes, or all nine genes) selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1, relative to a reference expression level, identifies the patient as having an increased likelihood of benefit from treatment with an IRAK4 pathway inhibitor.

In some embodiments, the reference expression level can be: (i) the expression level of the one or more genes set forth in Table 1 in a reference population (e.g., a median expression level of the one or more genes set forth in Table 1 in a reference population); or (ii) a pre-assigned expression level for the one or more genes set forth in Table 1.

In any of the above methods, administration of an IRAK4 pathway inhibitor can have the therapeutic effect (i.e., benefit) of a cellular or biological response, a complete response, a partial response, a stable disease (without progression or relapse), or a response with a later relapse of the patient from, or as a result of, the treatment with the IRAK4 pathway inhibitor. Responsiveness to treatment with the IRAK4 pathway inhibitor will be evaluated and assessed by different means in accordance with standard medical practice for the specific IRAK4-mediated disorder or condition.

Generally, the physician of skill will look for reduction in the signs and symptoms of the specific disease. The following are by way of examples.

For the IRAK4-mediated disorders of lupus and SLE, SLEDAI scores provide a numerical quantitation of disease activity. The SLEDAI is a weighted index of 24 clinical and laboratory parameters known to correlate with disease activity, with a numerical range of 0-103. see Bryan Gescuk & John Davis, "Novel therapeutic agent for systemic lupus erythematosus" in Current Opinion in Rheumatology 2002, 14:515-521. Antibodies to double-stranded DNA are believed to cause renal flares and other manifestations of lupus. Patients undergoing antibody treatment can be monitored for time to renal flare, which is defined as a significant, reproducible increase in serum creatinine, urine protein or blood in the urine. Alternatively or in addition, patients can be monitored for levels of antinuclear antibodies and antibodies to double-stranded DNA.

For the IRAK4-mediated disorder of rheumatoid arthritis (RA), measurements for progress in treatment may include the number of swollen and tender joints and the length of morning stiffness. Patients may be examined for how much the joint in the hands and feet have eroded by using X-rays and a scoring system known as the Sharp score. Another scoring system is based on the American College of Rheumatology criteria for assessing response to therapies. One method of evaluating treatment efficacy in RA is based on American College of Rheumatology (ACR) criteria, which measures the percentage of improvement in tender and swollen joints, among other things. The RA patient can be scored at for example, ACR 20 (20 percent improvement) compared with no antibody treatment (e.g,, baseline before treatment) or treatment with placebo. Other ways of evaluating the efficacy of antibody treatment include X-ray scoring such as the Sharp X-ray score used to score structural damage such as bone erosion and joint space narrowing. Patients can also be evaluated for the prevention of or improvement in disability based on Health Assessment Questionnaire [HAQ] score, AIMS score, SF-36 at time periods during or after treatment. The ACR 20 criteria may include 20% improvement in both tender (painful) joint count and swollen joint count plus a 20% improvement in at least 3 of 5 additional measures:

1. patient's pain assessment by visual analog scale (VAS),
2. patient's global assessment of disease activity (VAS),
3. physician's global assessment of disease activity (VAS),
4. patient's self-assessed disability measured by the Health Assessment Questionnaire, and
5. acute phase reactants, CRP or ESR.

The ACR 50 and 70 are defined analogously. Preferably, the patient is administered an amount of a CD20 binding antibody of the invention effective to achieve at least a score of ACR 20, preferably at least ACR 30, more preferably at least ACR50, even more preferably at least ACR70, most preferably at least ACR 75 and higher.

In some instances, administration of an IRAK4 pathway inhibitor has the therapeutic effect of reducing or delaying progression of the IRAK4-mediated disorder or condition by 1 day or more (e.g., by 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months,

5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 1 year or more) compared to treatment that does not include an IRAK4 pathway inhibitor.

In any of the preceding therapeutic methods, the IRAK4-mediated disorder or condition is selected from the group consisting of an immune disorder, an inflammatory disorder, a fibrotic disorder, an eosinophilic disorder, an infection, pain, a central nervous system disorder, an acute kidney injury, a chronic kidney disease, endometriosis, non-alcoholic fatty liver disease, a metabolic syndrome, and obesity.

In some instances, the immune disorder is allergic airway syndrome, allergic rhinitis, allograft rejection, asthma, atopic dermatitis, contact dermatitis, Crohn's disease, cutaneous lupus, delayed hypersensitivity, diabetes, gout, graft versus host disease, graft rejection, inflammatory bowel disease (IBD), inflammatory myositis (e.g., polymyositis, dermatomyositis), lupus, lupus nephritis, multiple sclerosis, psoriasis, rheumatoid arthritis, scleroderma, sepsis, systemic lupus erythematosus, systemic sclerosis, or ulcerative colitis.

In some instances, the inflammatory disorder is acute respiratory distress syndrome, acute lung injury, adult onset Still's disease, allergic airway syndrome, allergic rhinitis, asthma, atherosclerosis, atopic dermatitis, bronchitis, calcium pyrophosphate deposition disease (CPPD), cerebrovascular accident (e.g., stroke), chronic obstructive pulmonary disease (COPD), contact dermatitis, Crohn's disease, cryopyrin-associated periodic syndromes (CAPS), cutaneous lupus, delayed hypersensitivity, gout, graft versus host disease, inflammatory bowel disease (IBD), inflammatory myositis (e.g., polymyositis, dermatomyositis), lupus, lupus nephritis, rheumatoid arthritis, rhinitis, scleroderma, sepsis, systemic lupus erythematosus, systemic onset juvenile idiopathic arthritis, systemic sclerosis, or ulcerative colitis.

In some instances, the eosinophilic disorder is allergic rhinitis, asthma, atopic dermatitis, chronic obstructive pulmonary disease (COPD), or contact dermatitis.

In some instances, the fibrotic disorder is atherosclerosis, scleroderma, or systemic sclerosis.

In some instances, the central nervous system disorder is cerebrovascular accident (e.g., stroke), multiple sclerosis, or neurodegeneration.

In some instances, the pain is neuropathic pain.

In some instances, the infection is bronchitis or sepsis.

As described above, the IRAK4 pathway inhibitor may be an IRAK4 inhibitor, an IRAK1 inhibitor, a toll-like receptor (TLR) inhibitor, an interleukin-1 receptor (IL-1R) inhibitor, an interleukin-33 receptor (IL-33R) inhibitor, or a myeloid differentiation primary response gene 88 (MyD88) inhibitor. In one instance, the IRAK4 pathway inhibitor is an IRAK4 inhibitor. In some instances, the IRAK4 pathway inhibitor is a TLR inhibitor. In some instances, the TLR inhibitor is a TLR7 inhibitor, a TLR8 inhibitor, a TLR9 inhibitor, a TLR1 inhibitor, a TLR2 inhibitor, a TLR4 inhibitor, a TLR5 inhibitor, a TLR6 inhibitor, or a TLR10 inhibitor. In certain instances, the IRAK4 pathway inhibitor is a TLR7 inhibitor, a TLR8 inhibitor, or both a TLR7 and TLR8 inhibitor. In certain instances, the IRAK4 pathway inhibitor is a TLR9 inhibitor. In any one of the preceding embodiments, the IRAK4 pathway inhibitor is a small molecule inhibitor. In other embodiments, the IRAK4 pathway inhibitor is a protein or multi-protein complex, such as an antibody.

Dosage and Administration

Once a patient responsive or sensitive to treatment with an IRAK4 pathway inhibitor has been identified, treatment with the IRAK4 pathway inhibitor, alone or in combination with an additional therapeutic agent, can be carried out. Such treatment may result in, for example, reducing or delaying progression of the IRAK4-mediated disorder or condition by 1 day or more (e.g., by 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 1 year or more) compared to treatment that does not include an IRAK4 pathway inhibitor. Moreover, treatment with the combination of an IRAK4 pathway inhibitor and at least one additional therapeutic agent preferably results in an additive, more preferably synergistic (or greater than additive), therapeutic benefit to the patient. Preferably, in this combination method the timing between at least one administration of the IRAK4 pathway inhibitor and at least one additional therapeutic agent is about one month or less, and more preferably, about two weeks or less.

It will be appreciated by those of skill in the art that the exact manner of administering a therapeutically effective amount of an IRAK4 pathway inhibitor to a patient following diagnosis of their likely responsiveness to the IRAK4 pathway inhibitor will be at the discretion of the attending physician. The mode of administration, including dosage, combination with other agents, timing and frequency of administration, and the like, may be affected by the diagnosis of a patient's likely responsiveness to such IRAK4 pathway inhibitor, as well as the patient's condition and history. Thus, even patients having IRAK4-mediated disorders or conditions (e.g., immune disorders (e.g., SLE) or inflammatory disorders (e.g., asthma)) who are predicted to be relatively insensitive to an IRAK4 pathway inhibitor may still benefit from treatment therewith, particularly in combination with other agents, including agents that may alter a patient's responsiveness to the antagonist.

A composition comprising an IRAK4 pathway inhibitor will be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular type of IRAK4-mediated disorder or condition being treated (e.g., immune disorder, inflammatory disorder, fibrotic disorder, eosinophilic disorder, infection, pain, central nervous system disorder, acute kidney injury, chronic kidney disease, endometriosis, non-alcoholic fatty liver disease, metabolic syndrome, and obesity), the particular mammal being treated (e.g., human), the clinical condition of the individual patient, the cause of the IRAK4-mediated disorder or condition, the site of delivery of the agent, possible side-effects, the type of inhibitor, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The effective amount of the IRAK4 pathway inhibitor to be administered will be governed by such considerations.

A physician having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required, depending on such factors as the particular type of IRAK4 pathway inhibitor used. For example, the physician could start with doses of such an IRAK4 pathway inhibitor, employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. The effectiveness of a given dose or treatment regimen of the inhibitor can be determined, for example, by assessing signs and symptoms in the patient using standard measures of efficacy.

In certain examples, the IRAK4 pathway inhibitor may be the only agent administered to the subject (i.e., as a monotherapy).

In certain examples, the patient is treated with the same IRAK4 pathway inhibitor at least twice. Thus, the first and second doses of the IRAK4 pathway inhibitor are preferably with the same IRAK4 pathway inhibitor (or at least the same class/type of IRAK4 pathway inhibitor, e.g., doses with the same or different IRAK4 inhibitor), and more preferably all doses of the IRAK4 pathway inhibitor are with the same IRAK4 pathway inhibitor, i.e., treatment for the first two doses, and preferably all doses, is with one class/type of IRAK4 pathway inhibitor (e.g., all doses with the same or different IRAK4 inhibitor).

Treatment with IRAK4 pathway inhibitors, or pharmaceutically acceptable salts thereof, can be carried out according to standard methods.

If multiple doses of an IRAK4 pathway inhibitor are provided, each dose may be provided using the same or a different administration means. In one embodiment, each dose is given by oral administration. In one embodiment, each dose is by intravenous administration. In another embodiment, each dose is given by subcutaneous administration. In yet another embodiment, the doses are given by both intravenous and subcutaneous administration.

The duration of therapy can be continued for as long as medically indicated or until a desired therapeutic effect (e.g., those described herein) is achieved. In certain embodiments, the therapy is continued for 1 month, 2 months, 4 months, 6 months, 8 months, 10 months, 1 year, 2 years, 3 years, 4 years, 5 years, or for a period of years up to the lifetime of the subject.

As noted above, however, these suggested amounts of IRAK4 pathway inhibitors are subject to a great deal of therapeutic discretion. The key factor in selecting an appropriate dose and scheduling is the result obtained, as indicated above. In some embodiments, the IRAK4 pathway inhibitor is administered as close to the first sign, diagnosis, appearance, or occurrence of the IRAK4-mediated disorder or condition being treated (e.g., immune disorder, inflammatory disorder, fibrotic disorder, eosinophilic disorder, infection, pain, central nervous system disorder, acute kidney injury, chronic kidney disease, endometriosis, non-alcoholic fatty liver disease, metabolic syndrome, and obesity) as possible.

1. Routes of Administration

IRAK4 pathway inhibitors and any additional therapeutic agents may be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular IRAK4-mediated disorder or condition being treated (e.g., immune disorder, inflammatory disorder, fibrotic disorder, eosinophilic disorder, infection, pain, central nervous system disorder, acute kidney injury, chronic kidney disease, endometriosis, non-alcoholic fatty liver disease, metabolic syndrome, and obesity), the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The IRAK4 pathway inhibitor need not be, but is optionally formulated with and/or administered concurrently with, one or more agents currently used to prevent or treat the IRAK4-mediated disorder or condition being treated (e.g., immune disorder, inflammatory disorder, fibrotic disorder, eosinophilic disorder, infection, pain, central nervous system

disorder, acute kidney injury, chronic kidney disease, endometriosis, non-alcoholic fatty liver disease, metabolic syndrome, and obesity).

For the prevention or treatment of an IRAK4-mediated disorder or condition being treated (e.g., immune disorder, inflammatory disorder, fibrotic disorder, eosinophilic disorder, infection, pain, central nervous system disorder, acute kidney injury, chronic kidney disease, endometriosis, non-alcoholic fatty liver disease, metabolic syndrome, and obesity), the appropriate dosage of an IRAK4 pathway inhibitor described herein (when used alone or in combination with one or more other additional therapeutic agents) will depend on the type of disease to be treated, the severity and course of the disease, whether the IRAK4 pathway inhibitor is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the IRAK4 pathway inhibitor, and the discretion of the attending physician. The IRAK4 pathway inhibitor is suitably administered to the patient at one time or over a series of treatments. For repeated administrations over several days or longer, depending on the condition, the treatment would generally be sustained until a desired suppression of disease symptoms occurs. Such doses may be administered intermittently, e.g., every week or every three weeks (e.g., such that the patient receives, for example, from about two to about twenty, or e.g., about six doses of the IRAK4 pathway inhibitor). An initial higher loading dose, followed by one or more lower doses may be administered. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

The IRAK4 pathway inhibitor can be administered by any suitable means, including orally, parenteral, topical, subcutaneous, intraperitoneal, intrapulmonary, intranasal, and/or intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Intrathecal administration is also contemplated. In addition, the IRAK4 pathway inhibitor may suitably be administered by pulse infusion, e.g., with declining doses of the IRAK4 pathway inhibitor.

If multiple doses of an IRAK4 pathway inhibitor are provided, each dose may be provided using the same or a different administration means. In one embodiment, each dose is by oral administration. For example, one or more IRAK4 pathway inhibitors can provided in tablet form. For example, one or more IRAK4 pathway inhibitors can be administered twice a day. In another embodiment, each exposure is given intravenously (i.v.). In another embodiment, each exposure is given by subcutaneous (s.c.) administration. In yet another embodiment, the exposures are given by both i.v. and s.c. administration.

2. Combination Therapy

The methods may further involve administering to the patient an effective amount of an IRAK4 pathway inhibitor in combination with an additional therapeutic agent. In some instances, the additional therapeutic agent is an additional IRAK4 pathway inhibitor. In some instances, the additional therapeutic agent is a corticosteroid, a nonsteroidal anti-inflammatory drug (NSAID), chloroquine, hydroxychloroquine (PLAQUENIL®), cyclosporine, azathioprine, methotrexate, mycophenolate mofetil (CELLCEPT®), or cyclophosphamide (CYTOXAN®). In some instances, the IRAK4 pathway inhibitor is used in combination with surgery.

The combination therapy may provide "synergy" and prove "synergistic," i.e., the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined, unit dosage formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially (i.e., serially), whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

As described above, the therapeutic methods may include administering a combination of two or more (e.g., three or more) IRAK4 pathway inhibitors. In some instances, for example, two IRAK4 inhibitors are administered in combination, either sequentially or concomitantly. In some instances, for example, two IRAK1 inhibitors are administered in combination, either sequentially or concomitantly. In some instances, for example, two TLR inhibitors are administered in combination, either sequentially or concomitantly. In some instances, for example, two IL-1R inhibitors are administered in combination, either sequentially or concomitantly. In some instances, for example, two IL-33R inhibitors are administered in combination, either sequentially or concomitantly. In some instances, for example, two MyD88 inhibitors are administered in combination, either sequentially or concomitantly.

In general, for the prevention or treatment of disease, the appropriate dosage of the additional therapeutic agent will depend on the type of disease to be treated, the type of antibody, the severity and course of the disease, whether the IRAK4 pathway inhibitor and additional agent (e.g., a corticosteroid) are administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the IRAK4 pathway inhibitor and additional agent, and the discretion of the attending physician. The IRAK4 pathway inhibitor and additional agent are suitably administered to the patient at one time or over a series of treatments. The IRAK4 pathway inhibitor is typically administered as set forth above. Depending on the type and severity of the disease, about 20 mg/m^2 to 600 mg/m^2 of the additional agent is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about or about 20 mg/m^2, 85 mg/m^2, 90 mg/m^2, 125 mg/m^2, 200 mg/m^2, 400 mg/m^2, 500 mg/m^2 or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. Thus, one or more doses of about 20 mg/m^2, 85 mg/m^2, 90 mg/m^2, 125 mg/m^2, 200 mg/m^2, 400 mg/m^2, 500 mg/m^2, 600 mg/m^2 (or any combination thereof) may be administered to the patient. Such doses may be administered intermittently, e.g., every week or every two, three weeks, four, five, or six (e.g., such that the patient receives from about two to about twenty, e.g., about six doses of the additional agent). An initial higher loading dose, followed by one or more lower doses may be administered. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

In one embodiment, the patient has never been previously administered any drug(s) to treat an IRAK4-mediated disorder or condition. In another embodiment, the patient have been previously

administered one or more medicaments(s) to treat an IRAK4-mediated disorder or condition. In a further embodiment, the patient was not responsive to one or more of the medicaments that had been previously administered to treat an IRAK4-mediated disorder or condition. Such drugs to which the subject may be non-responsive include, for example, one or more of a corticosteroid, a nonsteroidal anti-inflammatory drug (NSAID), chloroquine, hydroxychloroquine (PLAQUENIL®), cyclosporine, azathioprine, methotrexate, mycophenolate mofetil (CELLCEPT®), and/or cyclophosphamide (CYTOXAN®), not administered in combination with an IRAK4 pathway inhibitor.

VI. Diagnostic Kits and Compositions

The invention further provides diagnostic kits and compositions that include one or more reagents (e.g., polypeptides [such as antibodies or antigen-binding fragments thereof] or polynucleotides [such as probes or primers]) for determining the expression level of one or more genes (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 , 15, 16, 17, 18, 19, 20, 21, 22, 23, or all 24 genes) set forth in Table 1 in a sample from an individual or patient having an IRAK4-mediated disorder or condition (e.g., immune disorder, inflammatory disorder, fibrotic disorder, eosinophilic disorder, infection, pain, central nervous system disorder, acute kidney injury, chronic kidney disease, endometriosis, non-alcoholic fatty liver disease, metabolic syndrome, and obesity). In some instances, an increased expression level of the one or more genes set forth in Table 1, relative to a reference expression level, identifies a patient having an IRAK4-mediated disorder or condition who may benefit from treatment comprising the IRAK4 pathway inhibitor. In other instances, a decreased expression level of the one or more genes set forth in Table 1, relative to a reference expression level, identifies a patient having an IRAK4-mediated disorder or condition who may benefit from treatment comprising the IRAK4 pathway inhibitor. Optionally, the kit may further include instructions to use the kit to identify a patient with a higher likelihood of benefiting from treatment with an IRAK4 pathway inhibitor. In another instance, the kit may further include instructions to use the kit to select a medicament (e.g., a medicament including an IRAK4 pathway inhibitor, such as an IRAK4 inhibitor, an IRAK1 inhibitor, a toll-like receptor (TLR) inhibitor, an interleukin-1 receptor (IL-1R) inhibitor, an interleukin-33 receptor (IL-33R) inhibitor, or a myeloid differentiation primary response gene 88 (MyD88) inhibitor, or combinations thereof) for treating a patient having an IRAK4-mediated disorder or condition if the patient is treatment naïve and has an increased expression level of the one or more genes set forth in Table 1, relative to a reference expression level. In another instance, the kit may further include instructions to use the kit to select a medicament (e.g., a medicament including an IRAK4 pathway inhibitor, such as an IRAK4 inhibitor, an IRAK1 inhibitor, a toll-like receptor (TLR) inhibitor, an interleukin-1 receptor (IL-1R) inhibitor, an interleukin-33 receptor (IL-33R) inhibitor, or a myeloid differentiation primary response gene 88 (MyD88) inhibitor, or combinations thereof) for treating a patient having an IRAK4-mediated disorder or condition if the patient has a decreased expression level of the one or more genes set forth in Table 1, relative to a reference expression level, after receiving a first dose of a treatment including an IRAK4 pathway inhibitor.

The compositions of the invention include polypeptides (e.g., antibodies or antigen-binding fragments thereof) or polynucleotides (e.g., probes and/or primers) capable of determining the expression level of RNASE4 and, optionally one or more other biomarkers (e.g., PSA and/or ANG).

EXAMPLES

The following examples are provided to illustrate, but not to limit, the presently claimed invention.

Example 1. Identification of Genes with Impaired Response to TLR7/8 Stimulation in IRAK4-Deficient Patients

To determine candidate IRAK4 biomarker genes that can serve as both pharmacodynamic and predictive biomarkers, genes were first identified that displayed significantly lower induction following TLR stimulation in patients carrying loss-of-function IRAK4 mutations compared to healthy patients. To this end, an analysis of the microarray dataset of GEO Accession GSE25742 (Alsina et al. *Nat. Immunol.* 15:1134-42, 2014), a genome-wide microarray expression profiling study of whole blood from patients with defects in toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) (i.e., the Toll/IL-1 receptor (TIR) pathway) signaling, was performed. Analysis of the microarray dataset identified 285 genes that displayed significantly lower induction by the TLR7/8 stimulator R848 (resiquimod) in the whole blood from IRAK4-deficient patients compared to healthy patient controls (false discovery rate (FDR) < 0.05; fold-change (FC) > 1.25) (Figs. 1A-1B and 6). Whereas the healthy patient controls were found to upregulate type I interferons (IFNs) in response to R848, IRAK4$^{-/-}$ patients failed to upregulate type I IFNs and other TLR-regulated genes in response to R848 (Fig. 2).

Example 2. Identification of Genes Upregulated in Systemic Lupus Erythematosus (SLE) Patients

Analysis of two extra-renal systemic lupus erythematosus (SLE) patient cohorts was performed to determine which of the 285 differentially expressed genes identified in Example 1 also showed elevated baseline expression in SLE patients. Peripheral blood mononuclear cell (PBMC) microarray data (University of Michigan Cohort; SLE (n = 61), healthy controls (HC) (n =20)) and whole blood RNA sequencing data (ROSE Phase II Study (Kalunian et al. *Ann. Rheum. Dis.* 75: 196-202, 2016); SLE (n = 103), HC (n = 19)) were analyzed for differential expression between the SLE and HC groups in both datasets. 44 genes of the 285 differentially expressed genes were subsequently identified as upregulated in SLE patients compared to healthy patients in both datasets ($p < 0.05$; FC > 1.2) (Figs. 3 and 6).

Example 3. Characterization of IRAK4 Pathway Genes Using IRAK4 Kinase-Dead Mice

IRAK4 kinase-dead (KD) mice were generated to further characterize the putative IRAK4 pathway genes identified in Example 2. Genomic DNA for IRAK4 was isolated from a 129/J mouse genomic library using the 5' end of the mouse IRAK4 complementary DNA as a probe. Using standard cloning techniques, the targeting construct was designed to disrupt the ATG start codon and to replace part of exon 2 of the IRAK4 gene with a PGK-Neo cassette. The targeting plasmid was linearized and transfected into embryonic stem cells of a 129/Ola background (E14 clone). Homologously recombined embryonic stem cell lines were injected into day 3.5 C57BL/6J (B6) blastocysts that were subsequently transferred to CD1 pseudo-pregnant foster mothers to generate chimeric progeny. Male chimeras were back-crossed to C57BL/6J females to produce agouti progeny. Germline transmission in F1

heterozygous offspring was verified by Southern blot analysis, and the F1 heterozygotes were interbred to obtain homozygous mutant mice.

Bone marrow-derived macrophages (BMDMs) from the IRAK4 KD mice (n = 5) and wild-type control mice (n = 5) were harvested and stimulated *in vitro* for four hours with R848, a TLR7 agonist. Gene expression analyses were performed by Fluidigm for the putative IRAK4 pathway biomarker genes in unstimulated and stimulated BMDMs from IRAK4 KD and wild-type control mice. The gene expression analyses showed that the putative IRAK4 pathway biomarker genes displayed impaired induction by TLR7 in BMDMs from IRAK4 KD mice compared to IRAK4 wild-type mice (Figs. 4 and 6). Similar gene expression analyses of whole blood from human IRAK4$^{-/-}$ patients showed that certain putative IRAK4 pathway biomarker genes also displayed impaired induction by TLR7 (Fig. 6). In particular, 24 genes of the 44 total putative IRAK pathway biomarker genes were found to display impaired induction by TLR7 in both human and mouse. These 24 IRAK4 pathway biomarkers are listed in Table 1 and described herein and highlight the commonality between human and mouse systems.

Additional gene expression analyses demonstrated that IFNβ1 displayed a lower induction by R848 in IRAK4 KD mice compared to IRAK4 wild-type mice ($p = 0.02$) (Fig. 5). Other IFN-regulated genes (OAS1A, OAS2, IFIT1, IFNA5, and MX1) showed the same trend of decreased induction by R848 in IRAK4 KD mice compared to IRAK4 wild-type mice ($p < 0.15$) (Figs. 7A-7E).

Example 4. Dose-Dependent Downregulation of IRAK4 Pathway Biomarker Genes by IRAK4 Small Molecule Inhibitors

The 24 IRAK4 pathway biomarker genes were subsequently characterized based on inducibility by R848 and dose-dependent downregulation by two distinct IRAK4 small molecule inhibitor test compounds, G03074387 (G-4387) (BMS) and G03081557 (G-1557) (Pfizer), in human whole blood samples. Whole blood samples from three healthy donors were divided into six arms: (1) unstimulated; (2) stimulated with R848 at 1.25 μM (~440 ng/ml); (3) G-4387 at IC50 (268 nM) for 1 hour + R848 stimulation for 3.5 hours; (4) G-4387 at IC70 (553 nM) for 1 hour + R848 stimulation for 3.5 hours; (5) G-4387 at IC90 (1.75 μM) for 1 hour + R848 stimulation for 3.5 hours; and (6) G-4387 at 5 μM for 1 hour + R848 stimulation for 3.5 hours. Similar experiments were conducted using whole blood samples from the same three healthy donors for G-1557, except that the dose of G-1557 in Arms (3)-(6) were as follows: (3) G-1557 at IC50 (13 nM); (4) G-1557 at IC70 (25 nM); (5) G-1557 at IC90 (70 nM); and (6) G-1557 at 200 nM. For both experiments, RNA was subsequently extracted and transcript levels of the 24 IRAK4 pathway biomarker genes were measured by qPCR. The results of these experiments are shown in Figs. 8 and 9. Of the 24 IRAK4 pathway biomarker genes, nine genes (CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1) were dose-dependently downregulated by both G-4387 and G-1557 in whole blood (Fig. 9). In addition, an inter-correlated signature in SLE patient blood was observed for these IRAK4 biomarker genes in both ROSE Phase II and University of Michigan SLE Cohorts described above in Example 2 (Figs. 10A-10B). Significant positive correlations were also observed between IRAK4 pathway biomarker genes and interferon signature metric (ISM) and anti-dsDNA status, as well as levels of BAFF, anti-RNP antibodies, and anti-Sm antibodies. Significant

negative correlations were observed between the IRAK4 biomarker genes and levels of complement component 3 (C3) and complement component 4 (C4) in both SLE datasets.

Together, the data suggest that the coordinated expression of these IRAK4-regulated genes is reflective of TLR and other upstream stimulation and therefore reflects IRAK pathway activity, thereby supporting the utility of the identified IRAK4 pathway biomarker genes as pharmacodynamics and predictive diagnostic biomarkers for patients who are likely to respond to treatment including an IRAK4 pathway inhibitor (e.g., an IRAK4 small molecule inhibitor).

Other Embodiments

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by reference.

WHAT IS CLAIMED IS:

1. A method of monitoring the response of a patient having an interleukin-1 receptor-associated kinase 4 (IRAK4)-mediated disorder or condition to treatment comprising an IRAK4 pathway inhibitor, the method comprising:

(a) determining, in a sample obtained from the patient at a time point following administration of a first dose of the IRAK4 pathway inhibitor, the expression level of one or more genes set forth in Table 1; and

(b) comparing the expression level of the one or more genes set forth in Table 1 in the sample with a reference expression level, thereby monitoring the response of the patient to treatment comprising the IRAK4 pathway inhibitor.

2. The method of claim 1, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1.

3. The method of claim 2, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3.

4. The method of claim 3, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1.

5. The method of claim 4, wherein the one or more genes set forth in Table 1 comprises all nine of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1.

6. The method of claim 5, wherein the one or more genes set forth in Table 1 comprises all 11 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3.

7. The method of claim 6, wherein the one or more genes set forth in Table 1 comprises all 12 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1.

8. The method of claim 7, wherein the one or more genes set forth in Table 1 are all 24 genes set forth in Table 1.

9. The method of any one of claims 1-8, wherein the expression level of the one or more genes set forth in Table 1 is decreased in the sample obtained from the patient relative to the reference expression level.

10. The method of claim 9, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 0.5-fold relative to the reference expression level.

11. The method of claim 10, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 1-fold relative to the reference expression level.

12. The method of claim 11, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 2-fold relative to the reference expression level.

13. The method of claim 12, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 3-fold relative to the reference expression level.

14. The method of claim 13, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 4-fold relative to the reference expression level.

15. The method of claim 14, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 5-fold relative to the reference expression level.

16. The method of claim 15, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 10-fold relative to the reference expression level.

17. The method of any one of claims 9-16, wherein the decreased expression level of the one or more genes set forth in Table 1 indicates that the patient is responding to the IRAK4 pathway inhibitor.

18. The method of claim 17, further comprising administering at least a second dose of an IRAK4 pathway inhibitor to a patient whose expression level of the one or more genes set forth in Table 1 is decreased relative to the reference expression level.

19. A method of treating a patient having an IRAK4-mediated disorder or condition with an IRAK4 pathway inhibitor, the method comprising:

(a) determining, in a sample obtained from the patient at a time point following administration of a first dose of the IRAK4 pathway inhibitor, the expression level of one or more genes set forth in Table 1;

(b) comparing the expression level of the one or more genes set forth in Table 1 in the sample with a reference expression level; and

(c) administering at least a second dose of the IRAK4 pathway inhibitor to the patient based on a decreased expression level of the one or more genes set forth in Table 1 relative to the reference expression level.

20. The method of claim 19, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1.

21. The method of claim 20, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3.

22. The method of claim 21, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1.

23. The method of claim 22, wherein the one or more genes set forth in Table 1 comprises all nine of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1.

24. The method of claim 23, wherein the one or more genes set forth in Table 1 comprises all 11 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3.

25. The method of claim 24, wherein the one or more genes set forth in Table 1 comprises all 12 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1.

26. The method of claim 25, wherein the one or more genes set forth in Table 1 are all 24 genes set forth in Table 1.

27. The method of any one of claims 19-26, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 0.5-fold relative to the reference expression level.

28. The method of claim 27, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 1-fold relative to the reference expression level.

29. The method of claim 28, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 2-fold relative to the reference expression level.

30. The method of claim 29, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 3-fold relative to the reference expression level.

31. The method of claim 30, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 4-fold relative to the reference expression level.

32. The method of claim 31, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 5-fold relative to the reference expression level.

33. The method of claim 32, wherein the expression level of the one or more genes set forth in Table 1 is decreased at least about 10-fold relative to the reference expression level.

34. The method of any one of claims 1-33, wherein the reference expression level is:

(i) the expression level of the one or more genes set forth in Table 1 in a sample from the patient obtained prior to administration of the first dose of the IRAK4 pathway inhibitor;

(ii) the expression level of the one or more genes set forth in Table 1 in a reference population;

(iii) a pre-assigned expression level for the one or more genes set forth in Table 1;

(iv) the expression level of the one or more genes set forth in Table 1 in a sample obtained from the patient at a previous time point, wherein the previous time point is following administration of the first dose of the IRAK4 pathway inhibitor; or

(v) the expression level of the one or more genes set forth in Table 1 in a sample obtained from the patient at a subsequent time point.

35. A method of identifying a patient having an IRAK4-mediated disorder or condition who may benefit from treatment comprising an IRAK4 pathway inhibitor, the method comprising determining an expression level of one or more genes set forth in Table 1 in a sample obtained from the patient, wherein an increased expression level of the one or more genes set forth in Table 1 in the sample as compared to a reference expression level identifies the patient as one who may benefit from treatment comprising an IRAK4 pathway inhibitor.

36. A method of selecting a therapy for a patient having an IRAK4-mediated disorder or condition, the method comprising determining an expression level of one or more genes set forth in Table 1 in a sample obtained from the patient, wherein an increased expression level of the one or more genes set forth in Table 1 in the sample as compared to a reference expression level identifies the patient as one who may benefit from treatment comprising an IRAK4 pathway inhibitor.

37. The method of claim 35 or 36, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1.

38. The method of claim 37, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3.

39. The method of claim 38, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1.

40. The method of claim 39, wherein the one or more genes set forth in Table 1 comprises all nine of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1.

41. The method of claim 40, wherein the one or more genes set forth in Table 1 comprises all 11 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3.

42. The method of claim 41, wherein the one or more genes set forth in Table 1 comprises all 12 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1.

43. The method of claim 42, wherein the one or more genes set forth in Table 1 are all 24 genes set forth in Table 1.

44. The method of any one of claims 35-43, wherein the expression level of the one or more genes set forth in Table 1 is increased in the sample obtained from the patient relative to the reference expression level.

45. The method of claim 44, wherein the expression level of the one or more genes set forth in Table 1 is increased at least about 0.5-fold relative to the reference expression level.

46. The method of claim 45, wherein the expression level of the one or more genes set forth in Table 1 is increased at least about 1-fold relative to the reference expression level.

47. The method of claim 46, wherein the expression level of the one or more genes set forth in Table 1 is increased at least about 2-fold relative to the reference expression level.

48. The method of claim 47, wherein the expression level of the one or more genes set forth in Table 1 is increased at least about 3-fold relative to the reference expression level.

49. The method of claim 48, wherein the expression level of the one or more genes set forth in Table 1 is increased at least about 4-fold relative to the reference expression level.

50. The method of claim 49, wherein the expression level of the one or more genes set forth in Table 1 is increased at least about 5-fold relative to the reference expression level.

51. The method of claim 50, wherein the expression level of the one or more genes set forth in Table 1 is increased at least about 10-fold relative to the reference expression level.

52. The method of any one of claims 35-51, wherein the patient has an increased expression level of the one or more genes set forth in Table 1 relative to the reference expression level and the method further comprises administering to the patient an IRAK4 pathway inhibitor.

53. A method of treating a patient having an IRAK4-mediated disorder or condition, the method comprising administering to the patient an IRAK4 pathway inhibitor, wherein prior to treatment the expression level of one or more genes set forth in Table 1 in a sample obtained from the patient has been determined to be increased relative to a reference expression level.

54. The method of claim 53, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1.

55. The method of claim 54, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3.

56. The method of claim 55, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1.

57. The method of claim 56, wherein the one or more genes set forth in Table 1 comprises all nine of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1.

58. The method of claim 57, wherein the one or more genes set forth in Table 1 comprises all 11 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3.

59. The method of claim 58, wherein the one or more genes set forth in Table 1 comprises all 12 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1.

60. The method of claim 59, wherein the one or more genes set forth in Table 1 are all 24 genes set forth in Table 1.

61. The method of any one of claims 53-60, wherein the expression level of the one or more genes set forth in Table 1 have been determined to be increased at least about 0.5-fold relative to the reference expression level.

62. The method of claim 61, wherein the expression level of the one or more genes set forth in Table 1 have been determined to be increased at least about 1-fold relative to the reference expression level.

63. The method of claim 62, wherein the expression level of the one or more genes set forth in Table 1 have been determined to be increased at least about 2-fold relative to the reference expression level.

64. The method of claim 63, wherein the expression level of the one or more genes set forth in Table 1 have been determined to be increased at least about 3-fold relative to the reference expression level.

65. The method of claim 64, wherein the expression level of the one or more genes set forth in Table 1 have been determined to be increased at least about 4-fold relative to the reference expression level.

66. The method of claim 65, wherein the expression level of the one or more genes set forth in Table 1 have been determined to be increased at least about 5-fold relative to the reference expression level.

67. The method of claim 66, wherein the expression level of the one or more genes set forth in Table 1 have been determined to be increased at least about 10-fold relative to the reference expression level.

68. The method of any one of claims 35-67, wherein the reference expression level is:
(i) the expression level of the one or more genes set forth in Table 1 in a reference population; or
(ii) a pre-assigned expression level for the one or more genes set forth in Table 1.

69. The method of claim 34 or 68, wherein the expression level of the one or more genes set forth in Table 1 in a reference population is a median expression level of the one or more genes set forth in Table 1 in a reference population.

70. The method of any one of claims 1-69, wherein the sample obtained from the patient is a tissue sample, a whole blood sample, a plasma sample, or a serum sample.

71. The method of any one of claims 1-70, wherein the expression level is an mRNA expression level.

72. The method of claim 71, wherein the mRNA expression level is determined by RNA-Seq, qPCR, microarray analysis, gene expression profiling, serial analysis of gene expression, or whole genome sequencing.

73. The method of claim 72, wherein the mRNA expression level is determined by qPCR.

74. The method of any one of claims 1-70, wherein the expression level is a protein expression level.

75. The method of any one of claims 1-74, wherein the IRAK4-mediated disorder or condition is selected from the group consisting of an immune disorder, an inflammatory disorder, a fibrotic disorder, an eosinophilic disorder, an infection, pain, a central nervous system disorder, an acute kidney injury, a chronic kidney disease, endometriosis, non-alcoholic fatty liver disease, a metabolic syndrome, and obesity.

76. The method of claim 75, wherein the immune disorder is lupus, asthma, atopic dermatitis, rheumatoid arthritis, inflammatory bowel disease (IBD), Crohn's disease, or ulcerative colitis.

77. The method of claim 75, wherein the inflammatory disorder is lupus, asthma, atopic dermatitis, rheumatoid arthritis, inflammatory bowel disease (IBD), Crohn's disease, or ulcerative colitis.

78. The method of claim 76 or 77, wherein the lupus is systemic lupus erythematosus (SLE).

79. The method of claim 76 or 77, wherein the lupus is lupus nephritis.

80. The method of any one of claims 1-79, wherein the IRAK4 pathway inhibitor is an IRAK4 inhibitor, an IRAK1 inhibitor, a toll-like receptor (TLR) inhibitor, an interleukin-1 receptor (IL-1R) inhibitor, an interleukin-33 receptor (IL-33R) inhibitor, or a myeloid differentiation primary response gene 88 (MyD88) inhibitor.

81. The method of claim 80, wherein the IRAK4 pathway inhibitor is an IRAK4 inhibitor.

82. The method of claim 80, wherein the IRAK4 pathway inhibitor is a TLR inhibitor.

83. The method of claim 82, wherein the TLR inhibitor is a TLR7 inhibitor, a TLR8 inhibitor, a TLR9 inhibitor, a TLR1 inhibitor, a TLR2 inhibitor, a TLR4 inhibitor, a TLR5 inhibitor, a TLR6 inhibitor, or a TLR10 inhibitor.

84. The method of claim 83, wherein the TLR inhibitor is a TLR7 inhibitor, a TLR8 inhibitor, or both a TLR7 and TLR8 inhibitor.

85. The method of claim 83, wherein the TLR inhibitor is a TLR9 inhibitor.

86. The method of any one of claims 80-85, wherein the IRAK4 pathway inhibitor is a small molecule inhibitor.

87. The method of any one of claims 18-34 and 52-86, further comprising administering to the patient an additional therapeutic agent.

88. The method of claim 87, wherein the additional therapeutic agent is a corticosteroid, a nonsteroidal anti-inflammatory drug (NSAID), chloroquine, hydroxychloroquine (PLAQUENIL®), cyclosporine, azathioprine, methotrexate, mycophenolate mofetil (CELLCEPT®), or cyclophosphamide (CYTOXAN®).

89. The method of claim 87 or 88, wherein the IRAK4 pathway inhibitor and the additional therapeutic agent are co-administered.

90. The method of claim 87 or 88, wherein the IRAK4 pathway inhibitor and the additional therapeutic agent are sequentially administered.

91. A kit for identifying a patient having an IRAK4-mediated disorder or condition who may benefit from treatment comprising an IRAK4 pathway inhibitor, the kit comprising:

(a) polypeptides or polynucleotides capable of determining the expression level of one or more genes set forth in Table 1; and

(b) instructions for using the polypeptides or polynucleotides to identify a patient having an IRAK4-mediated disorder or condition who may benefit from treatment comprising the IRAK4 pathway inhibitor.

92. The kit of claim 91, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1.

93. The kit of claim 92, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3.

94. The kit of claim 93, wherein the one or more genes set forth in Table 1 comprises one or more genes selected from the group consisting of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1.

95. The kit of claim 94, wherein the one or more genes set forth in Table 1 comprises all nine of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, and SOCS1.

96. The kit of claim 95, wherein the one or more genes set forth in Table 1 comprises all 11 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, and PFKFB3.

97. The kit of claim 96, wherein the one or more genes set forth in Table 1 comprises all 12 of CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3, SOCS1, IL1RN, PFKFB3, and BCL2A1.

98. The kit of claim 97, wherein the one or more genes set forth in Table 1 are all 24 genes set forth in Table 1.

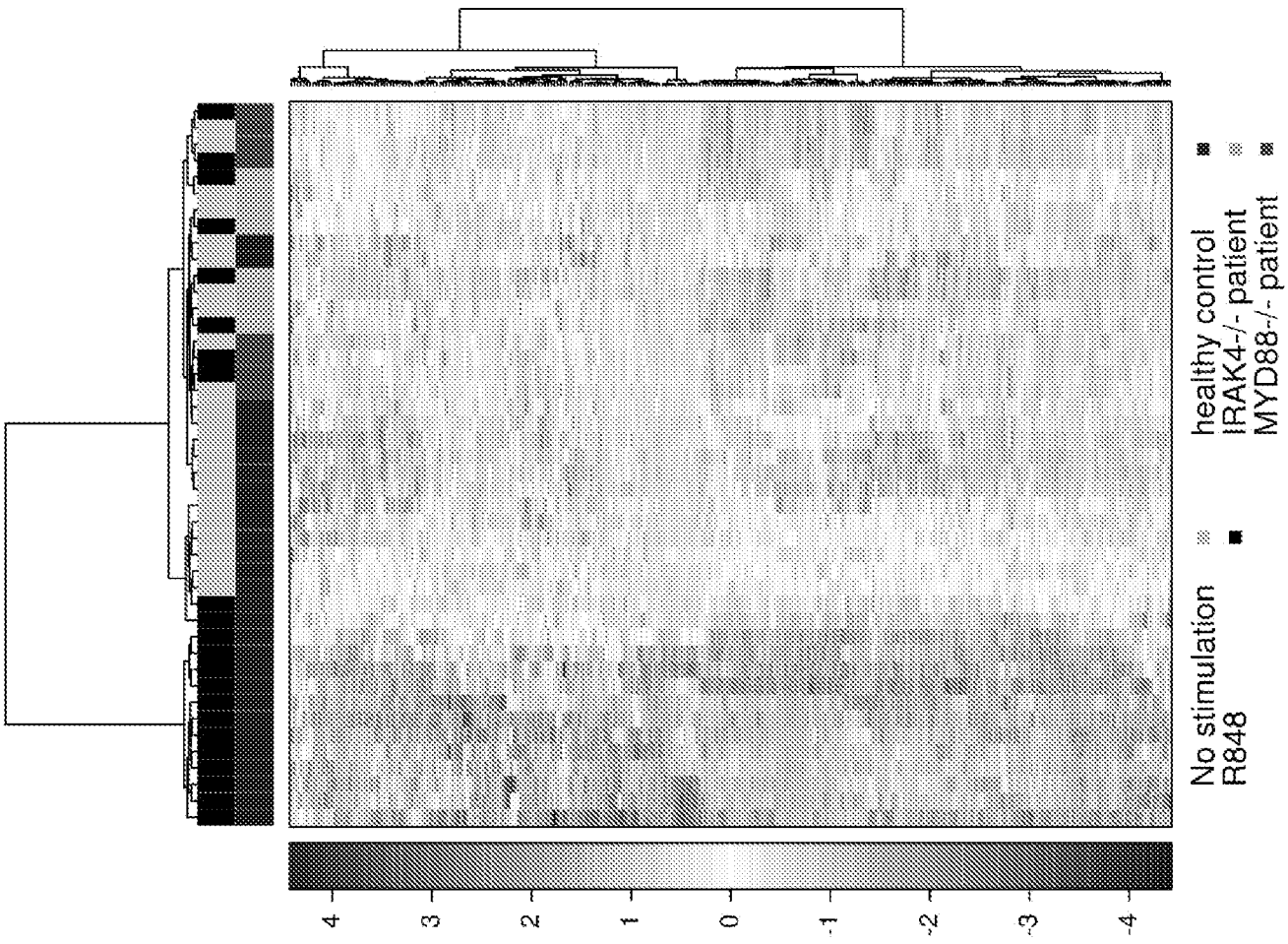

No stimulation
R848
healthy control
IRAK4-/- patient
MYD88-/- patient
4
3
2
1
0
-1
-2
-3
-4

FIG. 1A

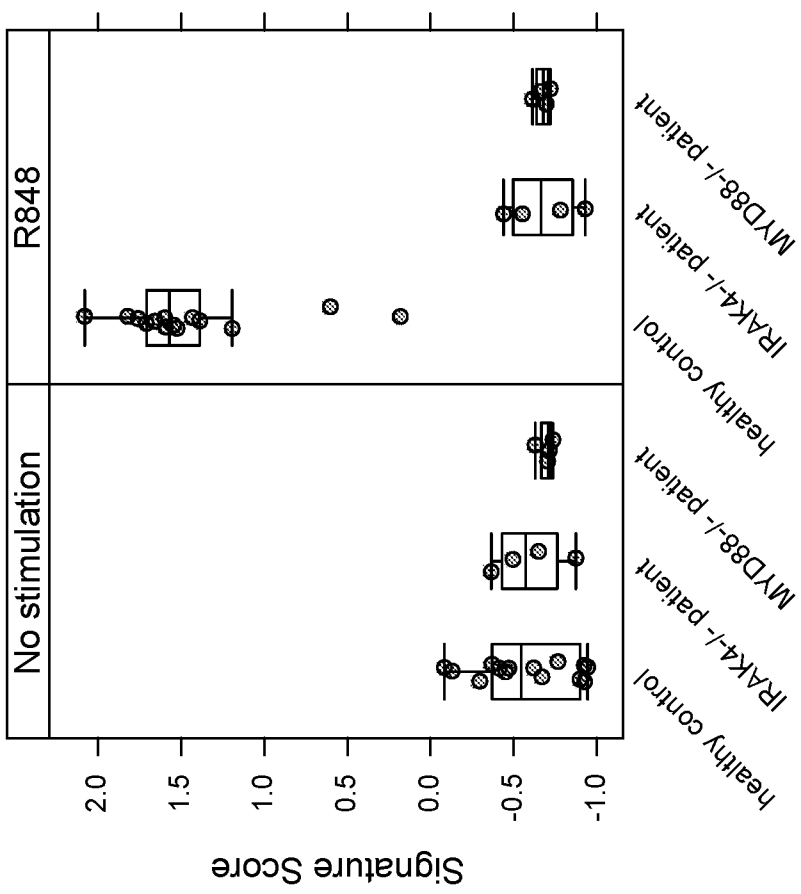

No stimulation
R848
Signature Score
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
healthy control
IRAK4-/- patient
MYD88-/- patient
healthy control
IRAK4-/- patient
MYD88-/- patient

FIG. 1B

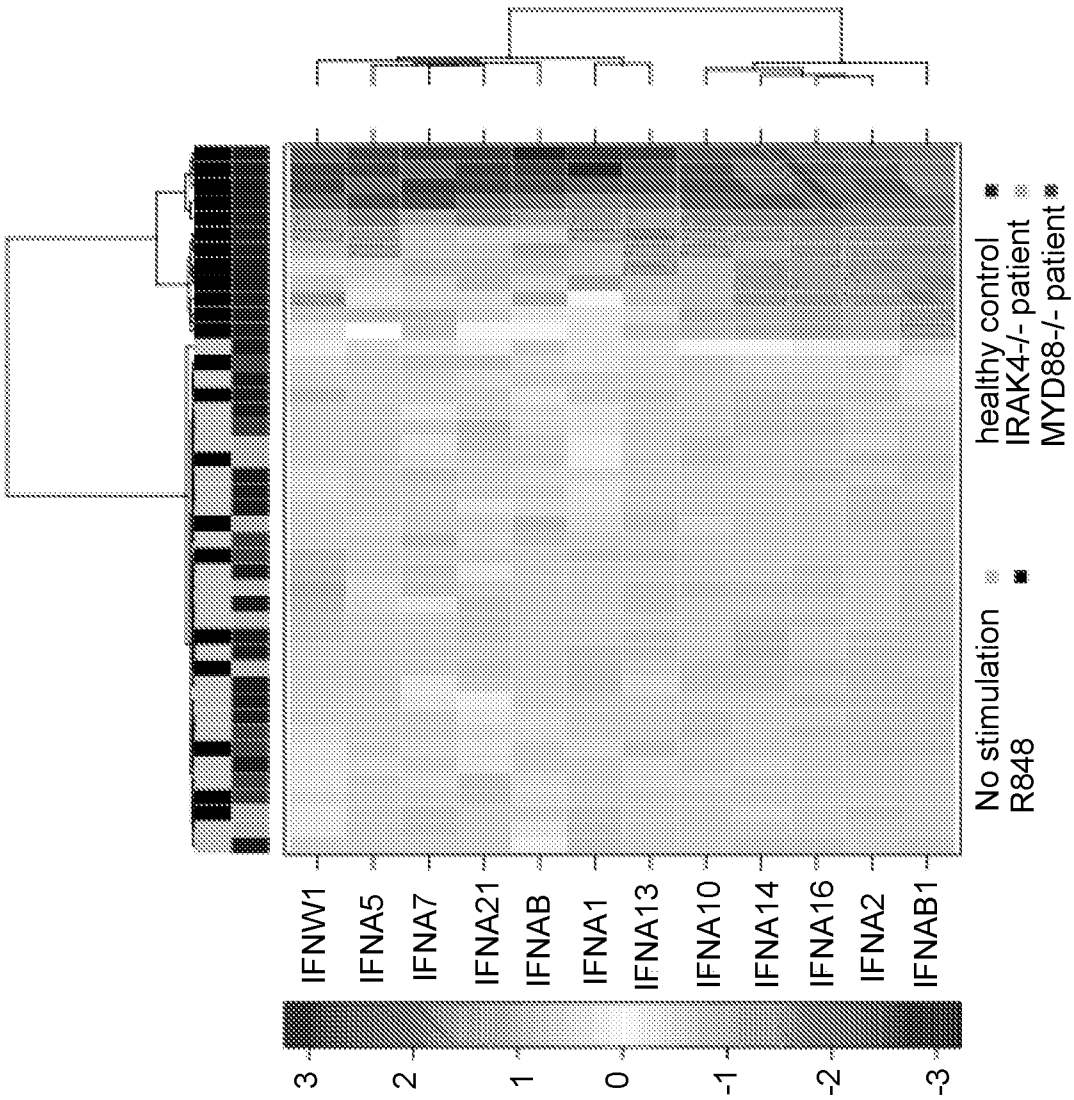
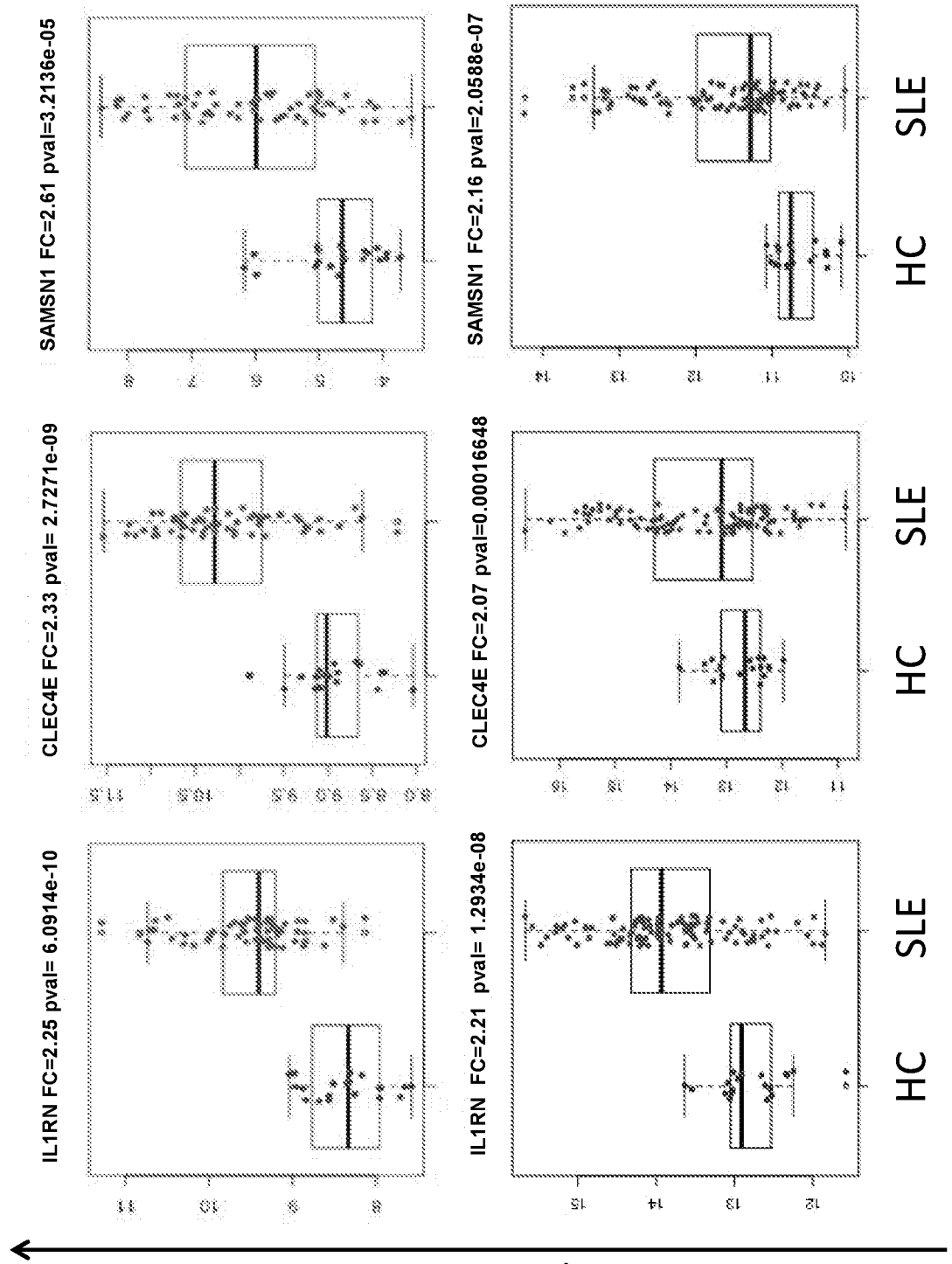

IFNW1
IFNA5
IFNA7
IFNA21
IFNAB
IFNA1
IFNA13
IFNA10
IFNA14
IFNA16
IFNA2
IFNAB1
3
2
1
0
-1
-2
-3
No stimulation
R848
healthy control
IRAK4-/- patient
MYD88-/- patient

FIG. 2

FIG. 3



Michigan
(Microarray SPR134;
SLE n=61; HC= 20)

ROSE
(RNAseq NGS 327;
SLE n=103; healthy= 19)

FIG. 4

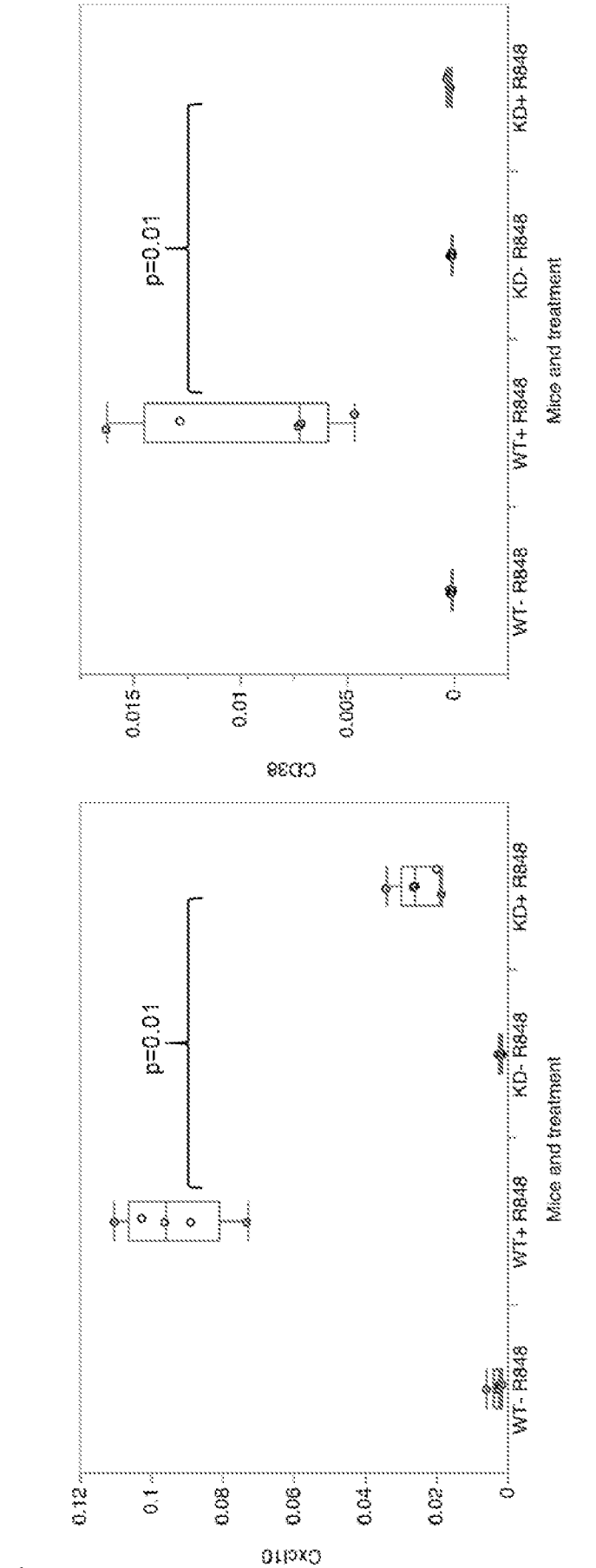

Gene expression (2^-dCt)
Cxcl10
0.12
0.1
0.08
0.06
0.04
0.02
0
p=0.01
WT- R848
WT+ R848
KD- R848
KD+ R848
Mice and treatment
CD38
0.015
0.01
0.005
0
p=0.01
WT- R848
WT+ R848
KD- R848
KD+ R848
Mice and treatment

FIG. 5

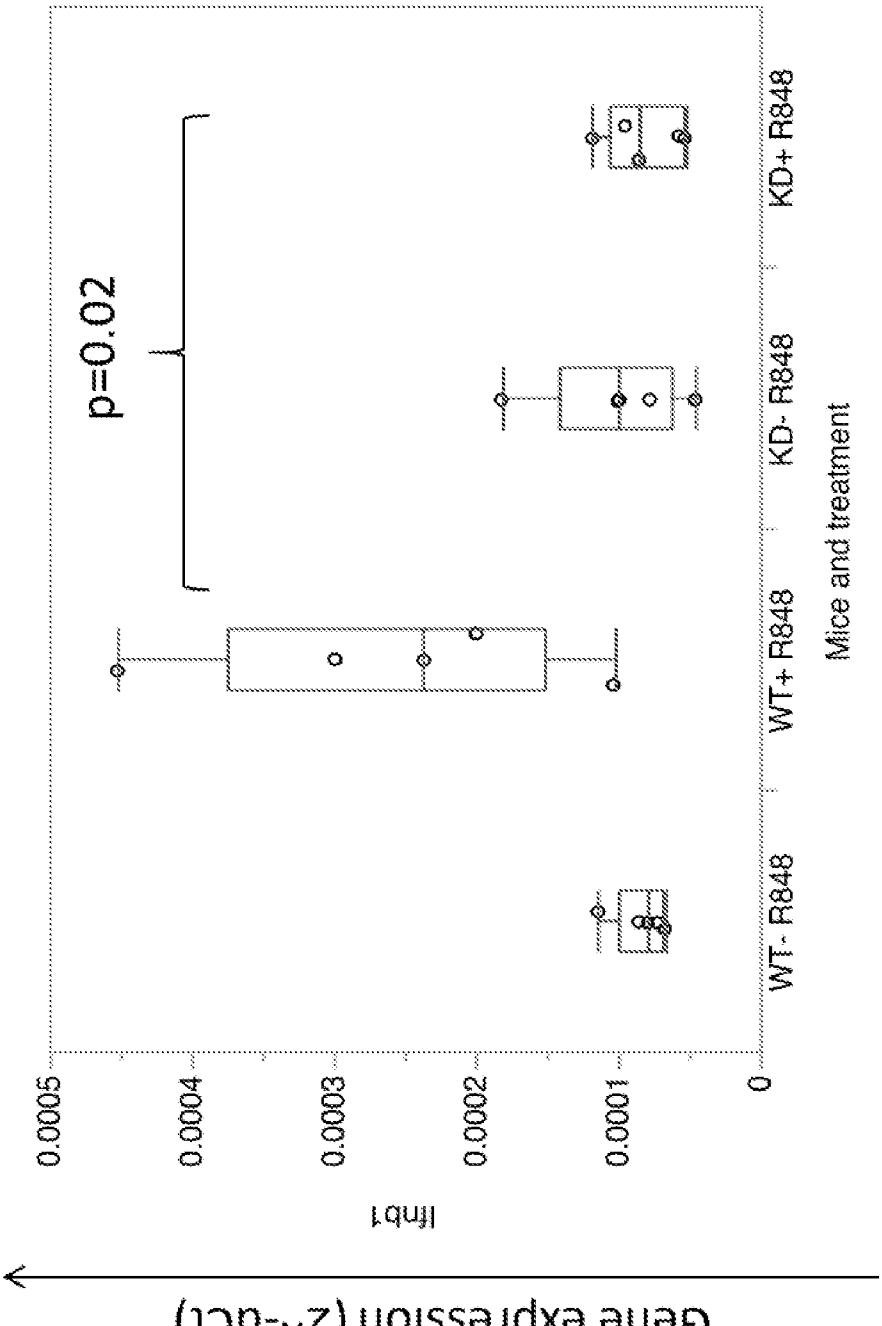

Gene expression (2^-dCt)
Ifnb1
0.0005
0.0004
0.0003
0.0002
0.0001
0
p=0.02
WT- R848
WT+ R848
KD- R848
KD+ R848
Mice and treatment

FIG. 6

	Impaired induction by R848 in Human IRAK4$^{-/-}$ WB		Impaired induction by R848 in IRAK4 KD mice macrophages	Elevated in SLE whole blood	
Genes	**Fold Change (log2) difference in HC vs. IRAK4-def.**	**p-value**	*Gene exp. ratio in KD vs. WT*	Fold Change (log2) (ROSE)	p-value (ROSE)
CXCL10	-6.21	0.0001	-2.77	1.99	2.5E-09
CCL8	-5.81	0.0002	-10.87	2.66	1.4E-09
IL1RN	-4.61	0.0000	-10.13	1.17	1.9E-08
GPR84	-3.72	0.0003	-3.81	0.89	9.5E-05
C15orf48	-3.68	0.0120	-5.36	1.59	1.2E-09
SOCS3	-2.96	0.0001	-7.66	0.57	1.8E-02
DRAM1	-2.93	0.0000	-3.63	0.47	6.2E-04
CXCL11	-2.79	0.0388	-8.10	2.2	1.2E-09
GADD45B	-2.6	0.0002	-5.44	0.77	3.2E-08
TNFAIP6	-2.53	0.0101	-9.21	1.72	1.0E-10
BCL2A1	-2.48	0.0217	-4.80	1.47	1.2E-09
SOCS1	-2.31	0.0005	-7.85	1.17	5.6E-07
TNFAIP3	-2.10	0.0001	-7.03	0.43	9.3E-04
CSRNP1	-2.07	0.0001	-1.90	0.74	6.9E-05
PLSCR1	-2.04	0.0165	-1.74	1.68	1.0E-10
CLEC4E	-2.01	0.0034	-4.77	1.09	2.6E-04
PFKFB3	-2.00	0.0018	-8.06	0.47	3.9E-02
CDKN1A	-1.82	0.0459	-2.97	0.39	4.2E-02
B4GALT5	-1.79	0.0013	-2.83	0.61	9.4E-06
CD38	-1.77	0.0006	-30.12	1.27	1.2E-06
SAMSN1	-1.55	0.0393	-5.39	1.14	3.1E-07
ACSL1	-1.51	0.0246	-4.03	0.77	1.8E-03
IL15RA	-1.39	0.0001	-1.91	0.49	6.9E-05
AQP9	-1.29	0.0060	-3.20	0.48	3.9E-02

FIG. 7A

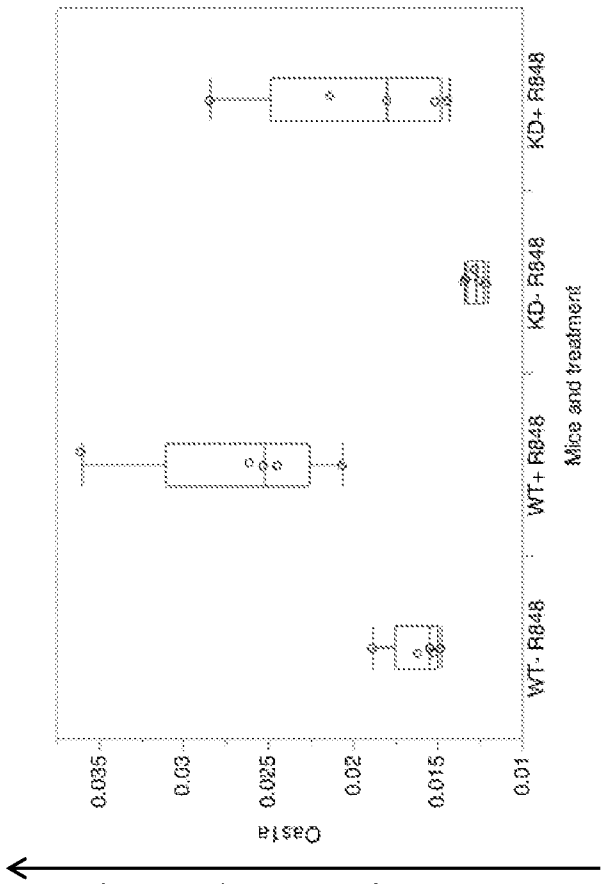

Gene expression (2^-dCt)
Oas1a
0.035
0.03
0.025
0.02
0.015
0.01
WT- R848
WT+ R848
KD- R848
KD+ R848
Mice and treatment

FIG. 7B

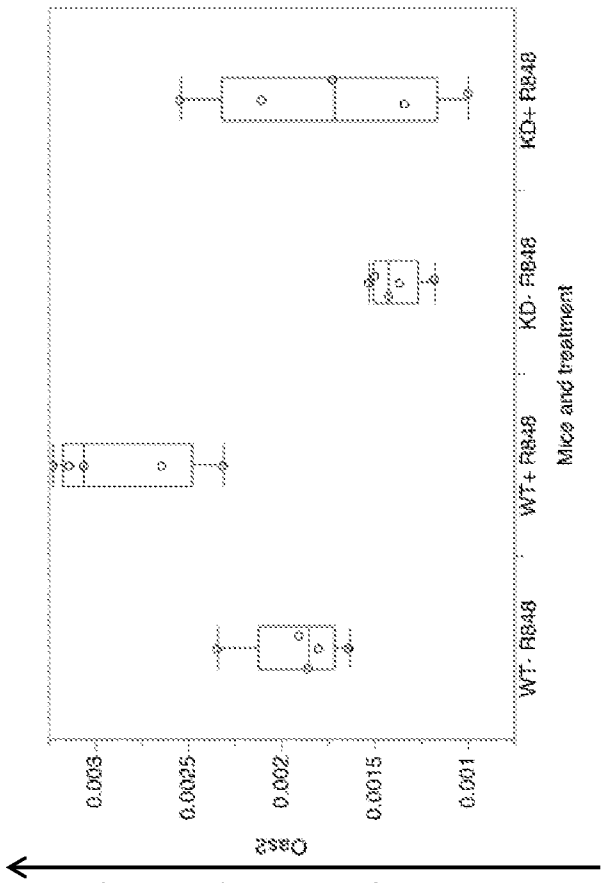

Gene expression (2^-dCt)
Oas2
0.003
0.0025
0.002
0.0015
0.001
WT- R848
WT+ R848
KD- R848
KD+ R848
Mice and treatment

FIG. 7C

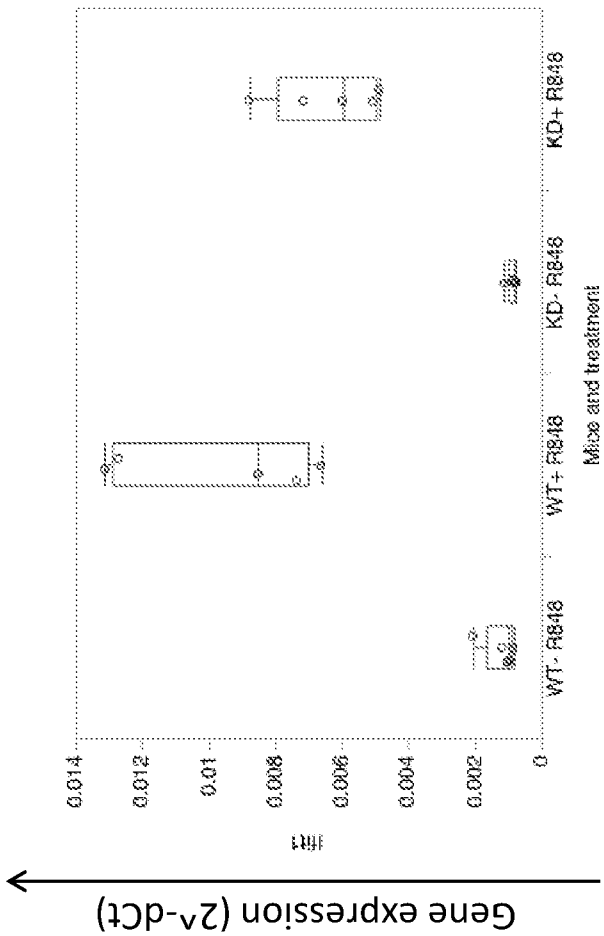
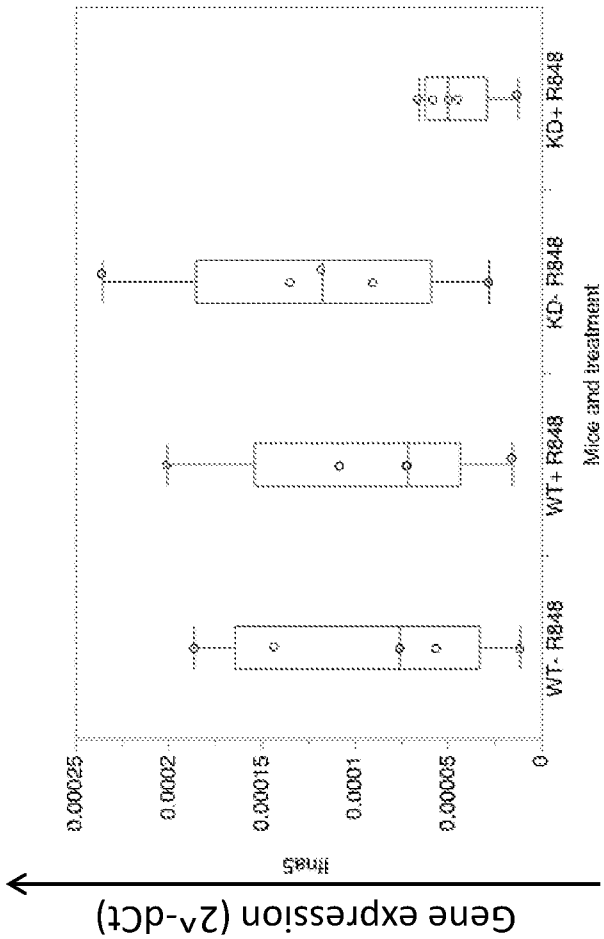

Gene expression (2^-dCt)
Ifit1
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
WT- R848
WT+ R848
KD- R848
KD+ R848
Mice and treatment

FIG. 7D


Gene expression (2^-dCt)
Ifnas
0.00025
0.0002
0.00015
0.0001
0.00005
0
WT- R848
WT+ R848
KD- R848
KD+ R848
Mice and treatment

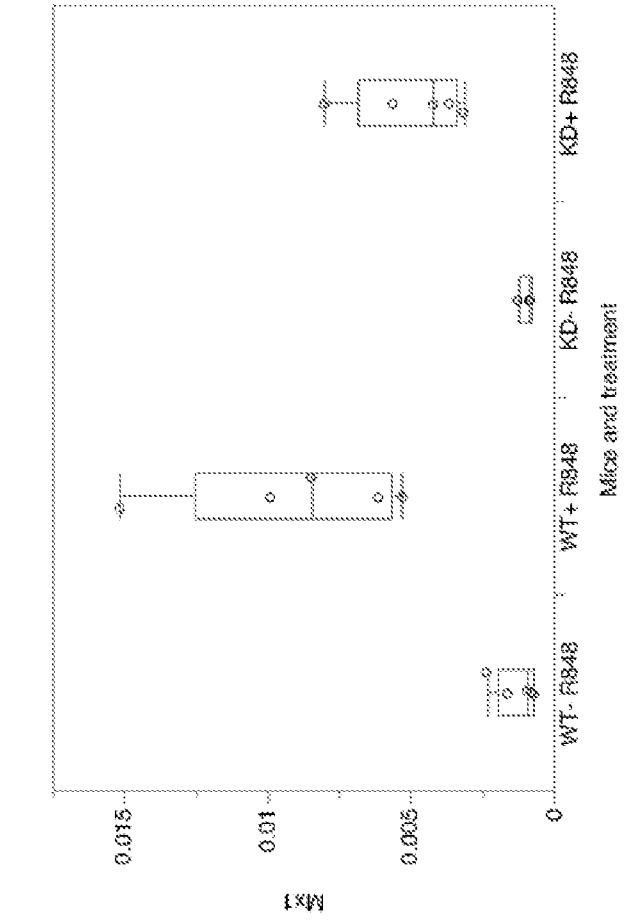

Gene expression (2^-dCt)
Mx1
0.015
0.01
0.005
0
WT- R848
WT+ R848
KD- R848
KD+ R848
Mice and treatment

FIG. 7E

FIG. 8

Genes	Dose-dep downregulation by G-4387 in at least 2 out of 3 donors	Dose-dep downregulation by G-1557 IRAK4i in at least 2 out of 3 donors
AQP9	Y	Y
B4GALT5	Y	Y
BCL2A1	Y	N
CD38	Y	Y
CDKN1A	Y	Y
GADD45B	Y	Y
IL15RA	Y	Y
IL1RN	Y	Y
PFKFB3	Y	Y
SOCS3	Y	Y
TNFAIP3	Y	Y
TNF	Y	Y
IL6	Y	Y
TNFAIP6	N	N
ACSL1	N	N
C15orf48	N	N
CCL8	N	N
CLEC4E	N	N
CSRNP1	N	N
CXCL10	N	N
CXCL11	N	N
DRAM1	N	N
GPR84	N	N
PLSCR1	N	N
SAMSN1	N	N
SOCS1	N	Y

Dose-dep downregulation in all 3 donors by respective SMI

FIG. 9

	G-4387 IC50 (268 nM)		G-4387 IC70 (553 nM)		G-4387 IC90 (1.75 uM)		G-4387 5 uM	
Gene	% decrease vs. control	p-value	% decrease vs. control	p-value	% decrease vs. control	p-value	% decrease vs. control	p-value
AQP9	0	1	-10.1	0.6	-31.7	0.2	-52	0.02*
B4GALT5	-9.2	0.5	-20	0.1	-27.4	0.07	-37.2	0.01*
SOCS1	-7.5	0.6	-6	0.6	-36.2	0.02*	-52.2	0.0005*
CD38	-16.9	0.1	-34.5	0.004*	-47.5	0.0008*	-47	0.0003*
CDKN1A	-7.2	0.6	-8.1	0.6	-24.8	0.2	-40.8	0.02*
GADD45B	-12.8	0.3	-18.2	0.2	-26.1	0.09	-38.6	0.008*
IL15RA	-4.8	0.8	-5.4	0.8	-18.4	0.4	-62.3	0.006*
SOCS3	-12.1	0.2	-26.2	0.004*	-56.3	<.0001*	-59.3	<.0001*
TNFAIP3	-7.9	0.5	-20.1	0.1	-35	0.02*	-50.3	0.0007*
TNF	-43.5	0.02*	-55.1	0.006*	-67.7	0.003*	-59.5	0.003*
IL6	-39.7	0.0006*	-53.2	<.0001*	-65	<.0001*	-54.2	<.0001*

	G-1557 IC50 (13 nM)		G-1557 IC70 (25 nM)		G-1557 IC90 (70 nM)		G-1557 200 nM	
Gene	% decrease vs. control	p-value	% decrease vs. control	p-value	% decrease vs. control	p-value	% decrease vs. control	p-value
AQP9	-41.1	0.05	-57.8	0.007*	-62.4	0.004*	-70	0.002*
B4GALT5	-26.7	0.05	-35.3	0.01*	-32.2	0.01*	-45.8	0.002*
SOCS1	-46.9	0.002*	-57.1	0.0003*	-55	0.0004*	-66.4	<.0001*
CD38	-13.3	0.2	-28.1	0.01*	-30.1	0.01*	-42.3	0.0008*
CDKN1A	-30.2	0.08	-51.9	0.005*	-43.5	0.02*	-61.7	0.001*
GADD45B	-25.8	0.06	-39.5	0.007*	-35.8	0.01*	-49.5	0.001*
IL15RA	-27.6	0.2	-51.8	0.02*	-48.5	0.03*	-57.2	0.01*
SOCS3	-43.3	<.0001*	-61.5	<.0001*	-59.9	<.0001*	-74.9	<.0001*
TNFAIP3	-42.7	0.003*	-57.1	0.0002*	-52.5	0.0004*	-62.2	<.0001*
TNF	*-28.5*	*0.1*	*-56.2*	0.005*	*-48.2*	0.01*	*-63.7*	0.002*
IL6	*-29*	0.007*	*-50.7*	<.0001*	*-52.4*	<.0001*	*-65*	<.0001*

Positive controls: TNFa and IL6. * significant p-value

FIG. 10A

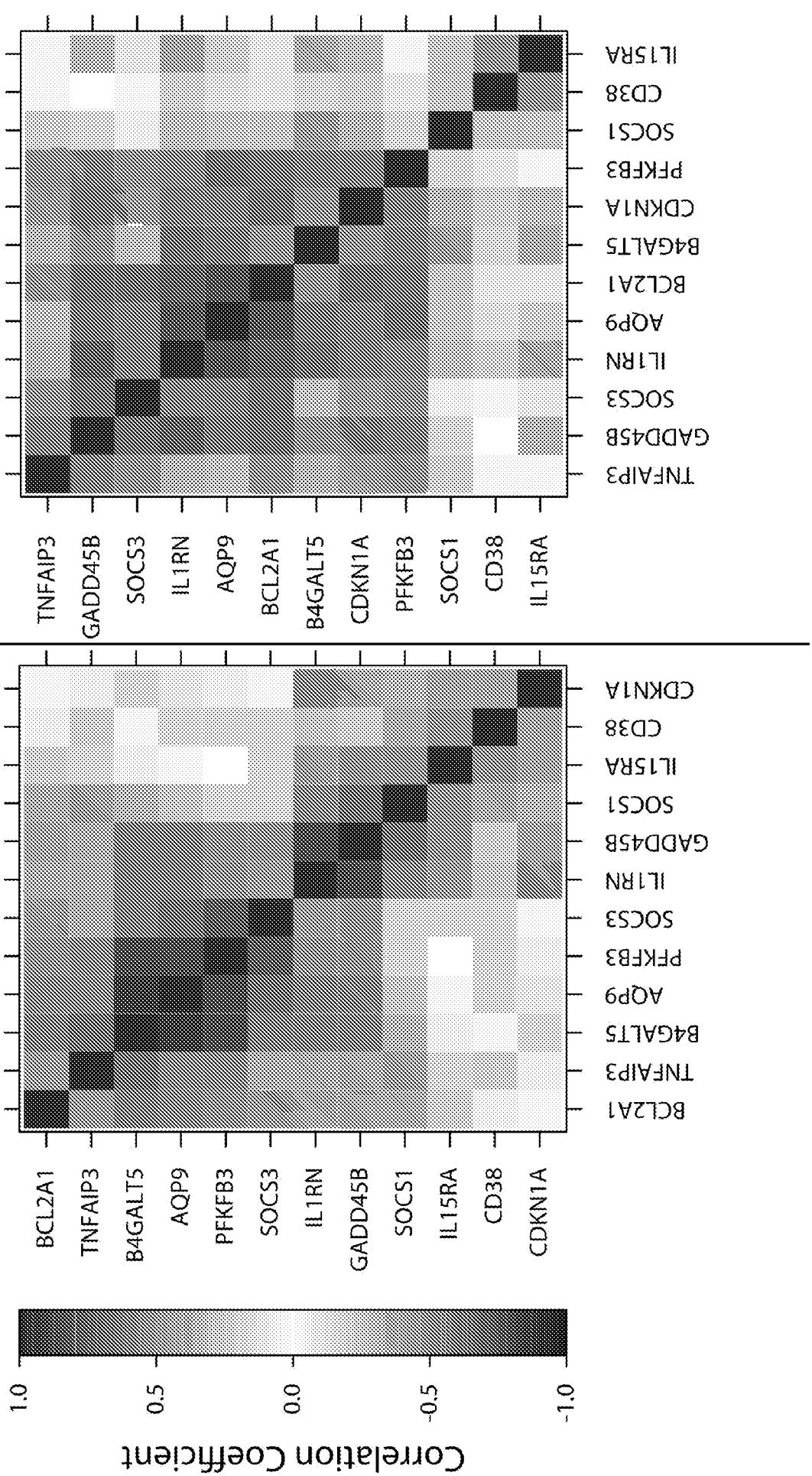


FIG. 10B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/037826

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-98(partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/037826

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/5377 G01N33/564
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K G01N

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	N.E. Genung ET AL: "Small Molecule Inhibition of Interleukin-1 Receptor-Associated Kinase 4 (IRAK4)" In: "PROGRESS IN MEDICINAL CHEMISTRY.", 1 January 2017 (2017-01-01), ELSEVIER, AMSTERDAM., NL, XP055503740, ISSN: 0079-6468 vol. 56, pages 117-163, DOI: 10.1016/bs.pmch.2016.11.004, paragraphs [1.3.1], [0002] -----	1-98
A	WO 2016/011390 A1 (BIOGEN MA INC [US]) 21 January 2016 (2016-01-21) claim 31 page 1, lines 5-6 ----- -/--	1-98

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 2018	01/10/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Herrmann, Klaus

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HYNES ET AL: "Advances in the Discovery of Small-Molecule IRAK4 Inhibitors", ANNUAL REPORTS IN MEDICINAL CHEMISTRY,, vol. 49, 1 January 2014 (2014-01-01), pages 117-133, XP009194732, DOI: 10.1016/B978-0-12-800167-7.00009-2 paragraphs [02.3], [02.5]	1-98
A	DIVYA CHAUDHARY ET AL: "Recent Advances in the Discovery of Small Molecule Inhibitors of Interleukin-1 Receptor-Associated Kinase 4 (IRAK4) as a Therapeutic Target for Inflammation and Oncology Disorders", JOURNAL OF MEDICINAL CHEMISTRY, vol. 58, no. 1, 8 January 2015 (2015-01-08), pages 96-110, XP055225289, ISSN: 0022-2623, DOI: 10.1021/jm5016044 the whole document	1-98
A	CHRISTOPHER G. HORTON ET AL: "Targeting Toll-Like Receptors for Treatment of SLE", MEDIATORS OF INFLAMMATION., vol. 2010, 1 January 2010 (2010-01-01), pages 1-9, XP055503916, GB ISSN: 0962-9351, DOI: 10.1155/2010/498980 abstract figure 1	1-98
A	EMILY C BAECHLER ET AL: "Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, US, vol. 100, no. 5, 4 March 2003 (2003-03-04) , pages 2610-2615, XP002622505, ISSN: 0027-8424, DOI: 10.1073/PNAS.0337679100 figure 2	1-98
A	ROZZO STEPHEN J ET AL: "Evidence for an interferon-inducible gene, Ifi202, in the susceptibility to systemic lupus", IMMUNITY, CELL PRESS, US, vol. 15, no. 3, 1 September 2001 (2001-09-01), pages 435-443, XP002292181, ISSN: 1074-7613, DOI: 10.1016/S1074-7613(01)00196-0 abstract	1-98

-/--

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FRANCK J. BARRAT ET AL: "Treatment of lupus-prone mice with a dual inhibitor of TLR7 and TLR9 leads to reduction of autoantibody production and amelioration of disease symptoms", EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 37, no. 12, 1 December 2007 (2007-12-01), pages 3582-3586, XP055108262, ISSN: 0014-2980, DOI: 10.1002/eji.200737815 page 3582, right-hand column, lines 3-4 page 3584, right-hand column, last paragraph - page 3585, left-hand column, paragraph 1 -----	1-98

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/037826

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016011390 A1	21-01-2016	AR 101229 A1	30-11-2016
		TW 201613872 A	16-04-2016
		US 2017204093 A1	20-07-2017
		WO 2016011390 A1	21-01-2016

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-98(partially)

1 Present application contains such a high number of independent claims (6 out of 98) that the application as a whole lacks conciseness (Rule 6.1(a) PCT). The plurality of independent claims, and additionally, the numerous alternatives contained within each independent claim makes it difficult, if not impossible, to determine the matter for which protection is sought. The application fails to comply with the requirements of Art. 6 PCT (conciseness) to such an extent that a meaningful search could not be carried out (Art. 17(2)(a)(ii) PCT).

2 Claims 1-98 fail to comply with the requirements of Art. 6 PCT (clarity) to such an extent that a meaningful search could not be carried out (Art. 17(2)(a)(ii) PCT).

2.1 The expression "interleukin-1 receptor-associated kinase 4 (IRAK4)-mediated disorder or condition" (e.g. claim 1) is unclear. Especially in view of original claim 75 said expression encompasses, for instance, any disease somehow mediated/connected/associated with inflammation, heart disease, obesity etc. For instance, an obese patient may well be depressed. Thus, in view of the broad expression used, e.g. depression is to be regarded as an "IRAK4-mediated disorder or condition". This one example alone makes clear that the skilled person does not know which diseases fall under said unclear expression.

2.2 The expression "IRAK4 pathway inhibitor" is unclear. In Fig. 1 of Chaudhary et al., 12/2014, for instance, discloses the IL1/TLR family ligand receptor signal transduction through IRAK4 and the myddosome complex. Do all the molecules shown in Fig. 1 of Chaudhary et al., 12/2014 belong to the so-called IRAK4 pathway or do more or less molecules play a role in such pathway?

3 Independent claims 1, 19, 35, 53 and 91 cover any disease falling under the expression "interleukin-1 receptor-associated kinase 4 (IRAK4)-mediated disorder or condition". Furthermore, said claims cover any "IRAK4 pathway inhibitor". However, the application provides support (Art. 6 PCT) and disclosure (Art. 5 PCT) for only a limited number of such inhibitors for use in the treatment of a limited number of diseases.

The examples only show a vague connection to systemic lupus erythematosus (SLE) (44 out of 285 genes in Example 2).

Furthermore, the only inhibitors that have been shown to have some effect on gene expression are two small molecule inhibitors of IRAK4 (9 out of 24 genes in Example 4).

4 In view of the above, a meaningful search over the whole of the scope claimed is impossible. Consequently, the search has been limited to methods and products comprising the following technical features (cf. Art. 17(2)(a)(ii) PCT):

- inhibitor of IRAK4
- one or more of the genes CD38, SOCS3, AQP9, CDKN1A, GADD45B,

B4GALT5, IL15RA, TNFAIP3 and SOCS1.
- disease = systemic lupus erythematosus (SLE)

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 110740733 A
(43)申请公布日 2020.01.31

(21)申请号 201880039467.3

(22)申请日 2018.06.15

(30)优先权数据
62/521,299 2017.06.16 US

(85)PCT国际申请进入国家阶段日
2019.12.13

(86)PCT国际申请的申请数据
PCT/US2018/037826 2018.06.15

(87)PCT国际申请的公布数据
WO2018/232288 EN 2018.12.20

(71)申请人 豪夫迈·罗氏有限公司
地址 瑞士巴塞尔

(72)发明人 J·哈克尼 A·F·塞蒂亚迪
M·汤森德 A·A·扎林

(74)专利代理机构 北京市中咨律师事务所 11247
代理人 陈迎春 黄革生

(51)Int.Cl.
A61K 31/5377(2006.01)
G01N 33/564(2006.01)

权利要求书6页 说明书51页
序列表85页 附图15页

(54)发明名称

IRAK4介导的疾患和病症的诊断和治疗方法

(57)摘要

本发明提供了用于治疗患有白介素-1受体相关激酶4(IRAK4)介导的疾患或病症,如免疫疾患(例如系统性红斑狼疮(SLE))或炎性疾患(例如哮喘)的患者的诊断性和治疗性方法和组合物。本发明提供了监测患有IRAK4介导的疾患或病症的患者对包括IRAK4通路抑制剂的治疗的反应的诊断方法、鉴定可从包括IRAK4通路抑制剂的治疗受益的患有IRAK4介导的疾患或病症的患者的方法、以及基于一个或多个IRAK4生物标志物(例如,表1中列出的一个或多个基因)的表达水平为患有IRAK4介导的疾患或病症的患者选择疗法的方法。还提供了相关的治疗方法和组合物(例如诊断试剂盒)。

CN 110740733 A

1.一种监测患有白介素-1受体相关激酶4(IRAK4)介导的疾患或病症的患者对包含IRAK4通路抑制剂的治疗之反应的方法,所述方法包括:

(a)在施用第一剂量IRAK4通路抑制剂后的时间点从患者获得的样品中,测定表1中列出的一个或多个基因的表达水平;和

(b)比较样品中表1中列出的一个或多个基因的表达水平与参考表达水平,从而监测患者对包含IRAK4通路抑制剂的治疗的反应。

2.根据权利要求1所述的方法,其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的一个或多个基因。

3.根据权利要求2所述的方法,其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的一个或多个基因。

4.根据权利要求3所述的方法,其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的一个或多个基因。

5.根据权利要求4所述的方法,其中表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的所有9个。

6.根据权利要求5所述的方法,其中表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的所有11个。

7.根据权利要求6所述的方法,其中表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的所有12个。

8.根据权利要求7所述的方法,其中,表1中列出的一个或多个基因是表1中列出的所有24个基因。

9.根据权利要求1-8中任一项所述的方法,其中,相对于参考表达水平,从患者获得的样品中表1中列出的一个或多个基因的表达水平降低。

10.根据权利要求9所述的方法,其中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约0.5倍。

11.根据权利要求10所述的方法,其中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约1倍。

12.根据权利要求11所述的方法,其中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约2倍。

13.根据权利要求12所述的方法,其中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约3倍。

14.根据权利要求13所述的方法,其中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约4倍。

15.根据权利要求14所述的方法,其中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约5倍。

16.根据权利要求15所述的方法,其中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约10倍。

17.根据权利要求9-16中任一项所述的方法，其中表1中列出的一个或多个基因的表达水平降低表明所述患者对IRAK4通路抑制剂反应。

18.根据权利要求17所述的方法，其进一步包括向表1中列出的一个或多个基因的表达水平相对于参考表达水平降低的患者施用至少第二剂量的IRAK4通路抑制剂。

19.一种用IRAK4通路抑制剂治疗患有IRAK4介导的疾患或病症的患者的方法，所述方法包括：

(a)在施用第一剂量IRAK4通路抑制剂后的时间点从患者获得的样品中，测定表1中列出的一个或多个基因的表达水平；

(b)比较样品中表1中列出的一个或多个基因的表达水平与参考表达水平；和

(c)基于表1中列出的一个或多个基因的表达水平相对于参考表达水平的降低，向患者施用至少第二剂量的IRAK4通路抑制剂。

20.根据权利要求19所述的方法，其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的一个或多个基因。

21.根据权利要求20所述的方法，其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的一个或多个基因。

22.根据权利要求21所述的方法，其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的一个或多个基因。

23.根据权利要求22所述的方法，其中表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的所有9个。

24.根据权利要求23所述的方法，其中表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的所有11个。

25.根据权利要求24所述的方法，其中表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的所有12个。

26.根据权利要求25所述的方法，其中表1中列出的一个或多个基因是表1中列出的所有24个基因。

27.根据权利要求19-26中任一项所述的方法，其中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约0.5倍。

28.根据权利要求27所述的方法，其中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约1倍。

29.根据权利要求28所述的方法，其中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约2倍。

30.根据权利要求29所述的方法，其中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约3倍。

31.根据权利要求30所述的方法，其中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约4倍。

32.根据权利要求31所述的方法，其中表1中列出的一个或多个基因的表达水平相对于

参考表达水平降低至少约5倍。

33.根据权利要求32所述的方法,其中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约10倍。

34.根据权利要求1至33中任一项所述的方法,其中所述参考表达水平是:

(i)在施用第一剂量的IRAK4通路抑制剂之前获得的患者样品中表1中列出的一个或多个基因的表达水平;

(ii)表1中列出的一个或多个基因在参考群中的表达水平;

(iii)表1中列出的一个或多个基因的预先指定的表达水平;

(iv)在先前时间点从患者获得的样品中表1中列出的一个或多个基因的表达水平,其中先前时间点在施用第一剂量IRAK4通路抑制剂之后;或

(v)在随后的时间点从患者获得的样品中表1列出的一个或多个基因的表达水平。

35.一种鉴定可从包含IRAK4通路抑制剂的治疗中受益的患有IRAK4介导的疾患或病症的患者的方法,所述方法包括测定从患者获得的样品中表1中列出的一个或多个基因的表达水平,其中与参考表达水平相比,样品中表1列出的一个或多个基因增加的表达水平鉴定该患者为可从包含IRAK4通路抑制剂的治疗中受益的患者。

36.为患有IRAK4介导的疾患或病症的患者选择疗法的方法,所述方法包括测定从患者获得的样品中表1中列出的一个或多个基因的表达水平,其中与参考表达水平相比,样品中表1中列出的一个或多个基因增加的表达水平鉴定该患者为可从包含IRAK4通路抑制剂的治疗中受益的患者。

37.根据权利要求35或36所述的方法,其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的一个或多个基因。

38.根据权利要求37所述的方法,其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的一个或多个基因。

39.根据权利要求38所述的方法,其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的一个或多个基因。

40.根据权利要求39所述的方法,其中表1列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的所有9个。

41.根据权利要求40所述的方法,其中表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的所有11个。

42.根据权利要求41所述的方法,其中表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的所有12个。

43.根据权利要求42所述的方法,其中表1中列出的一个或多个基因是表1中列出的所有24个基因。

44.根据权利要求35-43中任一项所述的方法,其中在从患者获得的样品中表1中列出的一个或多个基因的表达水平相对于参考表达水平增加。

45.根据权利要求44所述的方法,其中表1中列出的一个或多个基因的表达水平相对于

参考表达水平增加至少约0.5倍。

46.根据权利要求45所述的方法，其中表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约1倍。

47.根据权利要求46所述的方法，其中表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约2倍。

48.根据权利要求47所述的方法，其中表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约3倍。

49.根据权利要求48所述的方法，其中表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约4倍。

50.根据权利要求49所述的方法，其中表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约5倍。

51.根据权利要求50所述的方法，其中表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约10倍。

52.根据权利要求35-51中任一项所述的方法，其中所述患者具有相对于参考表达水平增加的表1中列出的一个或多个基因的表达水平，并且所述方法进一步包括向患者施用IRAK4通路抑制剂。

53.一种治疗患有IRAK4介导的疾患或病症的患者的方法，所述方法包括向所述患者施用IRAK4通路抑制剂，其中在治疗之前已经确定从患者获得的样品中表1中列出的一个或多个基因的表达水平相对于参考表达水平增加。

54.根据权利要求53所述的方法，其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的一个或多个基因。

55.根据权利要求54所述的方法，其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的一个或多个基因。

56.根据权利要求55所述的方法，其中表1列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的一个或多个基因。

57.根据权利要求56所述的方法，其中表1列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的所有九个。

58.根据权利要求57所述的方法，其中表1列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的所有11个。

59.根据权利要求58所述的方法，其中表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的所有12个。

60.根据权利要求59所述的方法，其中表1中列出的一个或多个基因是表1中列出的所有24个基因。

61.根据权利要求53-60中任一项所述的方法，其中已经确定表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约0.5倍。

62.根据权利要求61所述的方法，其中已经确定表1中列出的一个或多个基因的表达水

平相对于参考表达水平增加至少约1倍。

63.根据权利要求62所述的方法，其中已经确定表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约2倍。

64.根据权利要求63所述的方法，其中已经确定表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约3倍。

65.根据权利要求64所述的方法，其中已经确定表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约4倍。

66.根据权利要求65所述的方法，其中已经确定表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约5倍。

67.根据权利要求66所述的方法，其中已经确定表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约10倍。

68.根据权利要求35至67中任一项所述的方法，其中所述参考表达水平是：

(i)在参考群中表1中列出的一个或多个基因的表达水平；或

(ii)表1中列出的一个或多个基因的预先指定的表达水平。

69.根据权利要求34或68所述的方法，其中在参考群中表1中列出的一个或多个基因的表达水平是在参考群中表1中列出的一个或多个基因的中位表达水平。

70.根据权利要求1-69中任一项所述的方法，其中从患者获得的样品是组织样品、全血样品、血浆样品或血清样品。

71.根据权利要求1至70中任一项所述的方法，其中所述表达水平是mRNA表达水平。

72.根据权利要求71所述的方法，其中通过RNA-Seq、qPCR、微阵列分析、基因表达谱、基因表达的系列分析或全基因组测序来测定mRNA表达水平。

73.根据权利要求72所述的方法，其中通过qPCR测定mRNA表达水平。

74.根据权利要求1至70中任一项所述的方法，其中所述表达水平是蛋白质表达水平。

75.根据权利要求1-74中任一项所述的方法，其中所述IRAK4介导的疾患或病症选自免疫疾患、炎性疾患、纤维化疾患、嗜酸性细胞疾患、感染、疼痛、中枢神经系统疾患、急性肾脏损伤、慢性肾脏疾患、子宫内膜异位、非酒精性脂肪肝疾病、代谢综合征和肥胖症。

76.根据权利要求75所述的方法，其中所述免疫疾患是狼疮、哮喘、特应性皮炎、类风湿性关节炎、炎性肠疾病(IBD)、克罗恩氏病或溃疡性结肠炎。

77.根据权利要求75所述的方法，其中所述炎性疾患是狼疮、哮喘、特应性皮炎、类风湿性关节炎、炎性肠疾病(IBD)、克罗恩氏病或溃疡性结肠炎。

78.根据权利要求76或77所述的方法，其中所述狼疮是系统性红斑狼疮(SLE)。

79.根据权利要求76或77所述的方法，其中所述狼疮是狼疮肾炎。

80.根据权利要求1-79中任一项所述的方法，其中IRAK4通路抑制剂是IRAK4抑制剂、IRAK1抑制剂、toll样受体(TLR)抑制剂、白介素-1受体(IL-1R)抑制剂、白介素-33受体(IL-33R)抑制剂、或髓样分化主要反应基因88(MyD88)抑制剂。

81.根据权利要求80所述的方法，其中所述IRAK4通路抑制剂是IRAK4抑制剂。

82.根据权利要求80所述的方法，其中所述IRAK4通路抑制剂是TLR抑制剂。

83.根据权利要求82所述的方法，其中所述TLR抑制剂是TLR7抑制剂、TLR8抑制剂、TLR9抑制剂、TLR1抑制剂、TLR2抑制剂、TLR4抑制剂、TLR5抑制剂、TLR6抑制剂或TLR10抑制剂。

84.根据权利要求83所述的方法，其中所述TLR抑制剂是TLR7抑制剂、TLR8抑制剂或TLR7抑制剂和TLR8抑制剂两者。

85.根据权利要求83所述的方法，其中所述TLR抑制剂是TLR9抑制剂。

86.根据权利要求80-85中任一项所述的方法，其中所述IRAK4通路抑制剂是小分子抑制剂。

87.根据权利要求18-34和52-86中任一项所述的方法，其进一步包括向所述患者施用其他治疗剂。

88.根据权利要求87所述的方法，其中所述其他治疗剂是皮质类固醇、非类固醇抗炎药(NSAID)、氯喹、羟基氯喹(PLAQUENIL®)、环孢霉素、咪唑硫嘌呤、甲氨蝶呤、霉酚酸酯(CELLCEPT®)或环磷酰胺(CYTOXAN®)。

89.根据权利要求87或88所述的方法，其中所述IRAK4通路抑制剂和所述其他治疗剂共同施用。

90.根据权利要求87或88所述的方法，其中所述IRAK4通路抑制剂和所述其他治疗剂顺序施用。

91.一种试剂盒，其用于鉴定可以从包含IRAK4通路抑制剂的治疗中受益的患有IRAK4介导的疾患或病症的患者，所述试剂盒包含：

(a)能够测定表1中列出的一个或多个基因表达水平的多肽或多核苷酸；和

(b)使用所述多肽或多核苷酸鉴定可以从包含IRAK4通路抑制剂的治疗中受益的患有IRAK4介导的疾患或病症的患者的说明书。

92.根据权利要求91所述的试剂盒，其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的一个或多个基因。

93.根据权利要求92所述的试剂盒，其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的一个或多个基因。

94.根据权利要求93所述的试剂盒，其中表1列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的一个或多个基因。

95.根据权利要求94所述的试剂盒，其中表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的所有九个。

96.根据权利要求95所述的试剂盒，其中表1列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的所有11个。

97.根据权利要求96所述的试剂盒，其中表1列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的所有12个。

98.根据权利要求97所述的试剂盒，其中表1中列出的一个或多个基因是表1中列出的所有24个基因。

IRAK4介导的疾患和病症的诊断和治疗方法

[0001] 相关申请的交叉引用

[0002] 本申请要求于2017年6月16日提交的美国临时申请No.62/521,299的权益,其通过引用整体并入本文。

[0003] 序列表

[0004] 本申请包含序列表,该序列表以ASCII格式电子提交,并通过引用整体并入本文。所述ASCII副本创建于2018年6月14日,名称为50474-170WO2_Sequence_Listing_6.14.18_ST25,大小为142,784字节。

技术领域

[0005] 本发明涉及使用IRAK4通路抑制剂(例如IRAK4小分子抑制剂)用于治疗白介素-1受体相关激酶4(IRAK4)介导的疾患或病症(例如,免疫疾患(例如,系统性红斑狼疮(SLE))或炎性疾患(例如,哮喘))的诊断和治疗方法。还提供相关组合物(例如诊断试剂盒)。

背景技术

[0006] 白介素-1受体相关激酶(IRAK)家族由四个家族成员IRAK1、IRAK2、IRAK3(也称为IRAK-M)和IRAK4组成。这些蛋白质的特征在于典型的N末端死亡结构域和位于中心的激酶结构域,该死亡结构域介导与MyD88家族适体蛋白的相互作用。IRAK1和IRAK4具有激酶活性,而IRAK2和IRAK3无催化活性。当其上游同源受体激活后,认为IRAK4使IRAK1磷酸化,从而导致IRAK1的激活和自磷酸化,以及下游底物的随后磷酸化。IRAK1的过度磷酸化指导其从受体复合物中解离、以及其最终泛素化和蛋白酶体降解。下游底物(如Pellino-2)的磷酸化最终导致MAPK(如p38、c-Jun N末端激酶(JNK)和NF-kB)激活,随后产生促炎性细胞因子、趋化因子和破坏性酶。

[0007] IRAK4的作用,特别是其在先天免疫以及自身免疫和炎性疾患的发病机理中的作用被逐渐认识。参见,例如,Li等人PNAS.99(8):5567-5572,2002和Flannery等人Biochem.Pharm.80(12):1981-1991,2010。IRAK4不稳定或无效突变的患者表现出Toll样受体(TLR)信号传导和促炎性细胞因子(如IL-1和TNF)以及抗病毒细胞因子(如IFNα和IFNβ)产生的缺陷。这些患者表现出对革兰氏阳性细菌感染的易感性增加,尽管其通常对革兰氏阴性细菌、病毒和真菌感染具有抵抗力,类似地,IRAK4缺陷型小鼠在TLR和IL-1介导的细胞因子产生中具有缺陷,并且对感染表现出增加的易感性。毫不奇怪,IRAK4通路被认为参与多种疾患和病症,包括与IRAK介导的信号转导相关的炎性、免疫相关和细胞增殖性疾患和病症,对此仍存在开发改善的诊断方法的未满足的需求,以确定最适合治疗,包括IRAK4通路抑制剂(例如IRAK4小分子抑制剂)治疗的患者群。

发明内容

[0008] 本发明提供了用于治疗IRAK4介导的疾患或病症(例如,免疫疾患和炎性疾患)的诊断方法、治疗方法和试剂盒。

[0009] 在第一方面，本发明的特征在于监测患有白介素-1受体相关激酶4(IRAK4)介导的疾患或病症的患者对包含IRAK4通路抑制剂治疗的反应的方法，所述方法包括：(a)在施用第一剂量IRAK4通路抑制剂后的时间点从患者获得的样品中，测定表1中列出的一个或多个基因(即CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、BCL2A1、CXCL10、CCL8、GPR84、C15orf48、DRAM1、CXCL11、TNFAIP6、CSRNP1、PLSCR1、CLEC4E、SAMSN1和ACSL1)的表达水平，和(b)比较样品中表1中列出的一个或多个基因的表达水平与参考表达水平，从而监测患者对包含IRAK4通路抑制剂的治疗的反应。在一些实施方案中，表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的一个或多个基因。在一些实施方案中，表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的一个或多个基因。在一些实施方案中，表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的一个或多个基因。在一些实施方案中，表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的所有9个。在一些实施方案中，表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的所有11个。在一些实施方案中，表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的所有12个。在一些实施方案中，表1中列出的一个或多个基因是表1中列出的所有24个基因。

[0010] 在一些实施方案中，从患者获得的样品中表1中列出的一个或多个基因的表达水平相对于参考表达水平降低。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约0.5倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约1倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约2倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约3倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约4倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约5倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约10倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平降低表明患者对IRAK4通路抑制剂反应。在一些实施方案中，该方法进一步包括向表1中列出的一个或多个基因的表达水平相对于参考表达水平降低的患者施用至少第二剂量的IRAK4通路抑制剂。

[0011] 在第二方面，本发明的特征在于一种用IRAK4通路抑制剂治疗患有IRAK4介导的疾患或病症的患者的方法，该方法包括：(a)在施用第一剂量IRAK4通路抑制剂后的时间点从患者获得的样品中，测定表1中列出的一个或多个基因(即CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、BCL2A1、CXCL10、CCL8、GPR84、C15orf48、DRAM1、CXCL11、TNFAIP6、CSRNP1、PLSCR1、CLEC4E、SAMSN1和ACSL1)的表达水平，(b)比较样品中表1中列出的一个或多个基因的表达水平与参考表达水平，和(c)基于表1中列出的一个或多个基因的表达水平相对于参考表达水平的降低，向患者施用至少第二剂量的IRAK4通路抑制剂。在一些实施方案中，表1中列出的一个或多个基因包含选自CD38、

SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的一个或多个基因。在一些实施方案中，表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的一个或多个基因。在一些实施方案中，表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的一个或多个基因。在一些实施方案中，表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的所有9个。在一些实施方案中，表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的所有11个。在一些实施方案中，表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1的所有12个。在一些实施方案中，表1中列出的一个或多个基因是表1中列出的所有24个基因。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约0.5倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约1倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约2倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约3倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约4倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约5倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低至少约10倍。

[0012] 在前述方面中任一项的一些实施方案中，参考表达水平是：(i)在施用第一剂量的IRAK4通路抑制剂之前获得的患者样品中表1中列出的一个或多个基因的表达水平；(ii)表1中列出的一个或多个基因在参考群中的表达水平；(iii)表1中列出的一个或多个基因的预先指定的表达水平；(iv)在先前时间点从患者获得的样品中表1中列出的一个或多个基因的表达水平，其中先前时间点在施用第一剂量IRAK4通路抑制剂之后；或(v)在随后的时间点从患者获得的样品中表1列出的一个或多个基因的表达水平。

[0013] 在第三方面，本发明的特征在于鉴定可从包含IRAK4通路抑制剂的治疗中受益的患有IRAK4介导的疾患或病症的患者的方法，该方法包括测定从患者获得的样品中表1中列出的一个或多个基因的表达水平(即CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、BCL2A1、CXCL10、CCL8、GPR84、C15orf48、DRAM1、CXCL11、TNFAIP6、CSRNP1、PLSCR1、CLEC4E、SAMSN1和ACSL1)，其中与参考表达水平相比，样品中表1列出的一个或多个基因的表达水平增加，鉴定该患者为可从包含IRAK4通路抑制剂的治疗中受益的患者。

[0014] 在第四方面，本发明的特征在于一种为患有IRAK4介导的疾患或病症的患者选择疗法的方法，该方法包括测定从患者获得的样品中表1中列出的一个或多个基因的表达水平(即CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、BCL2A1、CXCL10、CCL8、GPR84、C15orf48、DRAM1、CXCL11、TNFAIP6、CSRNP1、PLSCR1、CLEC4E、SAMSN1和ACSL1)，其中与参考表达水平相比，样品中表1中列出的一个或多个基因的表达水平增加，鉴定该患者为可从包含IRAK4通路抑制剂的治疗中受益的患者。

[0015] 在第三或第四方面的一些实施方案中，表1中列出的一个或多个基因包含选自

CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的一个或多个基因。在一些实施方案中，表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的一个或多个基因。在一些实施方案中，表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的一个或多个基因。在一些实施方案中，表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的所有9个。在一些实施方案中，表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的所有11个。在一些实施方案中，表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的所有12个。在一些实施方案中，表1中列出的一个或多个基因是表1中列出的所有24个基因。在一些实施方案中，在从患者获得的样品中表1中列出的一个或多个基因的表达水平相对于参考表达水平增加。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约0.5倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约1倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约2倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约3倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约4倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约5倍。在一些实施方案中，表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约10倍。在一些实施方案中，患者具有相对于参考表达水平增加的表1中列出的一个或多个基因的表达水平，并且该方法进一步包括向患者施用IRAK4通路抑制剂。

[0016] 在第五方面，本发明的特征在于一种治疗患有IRAK4介导的疾患或病症的患者的方法，该方法包括向该患者施用IRAK4通路抑制剂，其中在治疗之前已经确定从患者获得的样品中表1中列出的一个或多个基因的表达水平(即CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、BCL2A1、CXCL10、CCL8、GPR84、C15orf48、DRAM1、CXCL11、TNFAIP6、CSRNP1、PLSCR1、CLEC4E、SAMSN1、和ACSL1)相对于参考表达水平增加。在一些实施方案中，表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的一个或多个基因。在一些实施方案中，表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的一个或多个基因。在一些实施方案中，表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的一个或多个基因。在一些实施方案中，表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的所有9个。在一些实施方案中，表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的所有11个。在一些实施方案中，表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的所有12个。在一些实施方案中，表1中列出的一个或多个基因是表1中列出的所有24个基因。在一些实施方案中，已经确

定表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约0.5倍。在一些实施方案中，已经确定表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约1倍。在一些实施方案中，已经确定表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约2倍。在一些实施方案中，已经确定表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约3倍。在一些实施方案中，已经确定表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约4倍。在一些实施方案中，已经确定表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约5倍。在一些实施方案中，已经确定表1中列出的一个或多个基因的表达水平相对于参考表达水平增加至少约10倍。

[0017] 在第三、第四和第五方面中任一项的一些实施方案中，参考表达水平是：(i)在参考群中表1中列出的一个或多个基因的表达水平；或(ii)表1中列出的一个或多个基因的预先指定的表达水平。

[0018] 在前述方面中任一项的一些实施方案中，在参考群中表1中列出的一个或多个基因的表达水平是在参考群中表1中列出的一个或多个基因的中位表达水平。

[0019] 在前述方面中任一项的一些实施方案中，从患者获得的样品是组织样品、全血样品、血浆样品或血清样品。在一些实施方案中，从患者获得的样品是血液样品(例如，全血样品)。

[0020] 在前述方面中任一项的一些实施方案中，表达水平是mRNA表达水平。在一些实施方案中，通过RNA-Seq、qPCR、微阵列分析、基因表达谱、基因表达的系列分析或全基因组测序来测定mRNA表达水平。在一些实施方案中，通过qPCR测定mRNA表达水平。在前述方面中任一项的其他实施方案中，表达水平是蛋白质表达水平。

[0021] 在前述方面中任一项的一些实施方案中，IRAK4介导的疾患或病症选自免疫疾患、炎性疾患、纤维化疾患、嗜酸性细胞疾患、感染、疼痛、中枢神经系统疾患、急性肾脏损伤、慢性肾脏疾患、子宫内膜异位、非酒精性脂肪肝疾病、代谢综合征和肥胖症。在一些实施方案中，免疫疾患是狼疮、哮喘、特应性皮炎、类风湿性关节炎、炎性肠疾病(IBD)、克罗恩氏病或溃疡性结肠炎。在一些实施方案中，炎性疾患是狼疮、哮喘、特应性皮炎、类风湿性关节炎、炎性肠疾病(IBD)、克罗恩氏病或溃疡性结肠炎。在一些实施方案中，狼疮是系统性红斑狼疮(SLE)。在一些实施方案中，狼疮是狼疮肾炎。

[0022] 在前述方面中任一项的一些实施方案中，IRAK4通路抑制剂是IRAK4抑制剂、IRAK1抑制剂、toll样受体(TLR)抑制剂、白介素-1受体(IL-1R)抑制剂、白介素-33受体(IL-33R)抑制剂、或髓样分化主要反应基因88(MyD88)抑制剂。在一些实施方案中，IRAK4通路抑制剂是IRAK4抑制剂。在一些实施方案中，IRAK4通路抑制剂是TLR抑制剂。在一些实施方案中，TLR抑制剂是TLR7抑制剂、TLR8抑制剂、TLR9抑制剂、TLR1抑制剂、TLR2抑制剂、TLR4抑制剂、TLR5抑制剂、TLR6抑制剂或TLR10抑制剂。在一些实施方案中，TLR抑制剂是TLR7抑制剂、TLR8抑制剂或TLR7和TLR8两者的抑制剂。在一些实施方案中，TLR抑制剂是TLR9抑制剂。在一些实施方案中，IRAK4通路抑制剂是小分子抑制剂。

[0023] 在前述方面中任一项的一些实施方案中，该方法进一步包括向患者施用其他治疗剂。在一些实施方案中，其他治疗剂是皮质类固醇、非类固醇抗炎药(NSAID)、氯喹、羟基氯喹(PLAQUENIL®)、环孢霉素、咪唑硫嘌呤、甲氨蝶呤、霉酚酸酯(CELLCEPT®)或环

磷酰胺(CYTOXAN®)。在一些实施方案中,IRAK4通路抑制剂和其他治疗剂共同施用。在一些实施方案中,IRAK4通路抑制剂和其他治疗剂顺序施用。

[0024] 在另一方面,本发明的特征在于一种试剂盒,其用于鉴定可以从包含IRAK4通路抑制剂的治疗中受益的患有IRAK4介导的疾患或病症的患者,所述试剂盒包含:(a)能够测定表1中列出的一个或多个基因表达水平的多肽或多核苷酸(即CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、BCL2A1、CXCL10、CCL8、GPR84、C15orf48、DRAM1、CXCL11、TNFAIP6、CSRNP1、PLSCR1、CLEC4E、SAMSN1和ACSL1);和(b)使用所述多肽或多核苷酸鉴定可以从包含IRAK4通路抑制剂的治疗中受益的患有IRAK4介导的疾患或病症的患者的说明书。在一些实施方案中,表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的一个或多个基因。在一些实施方案中,表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的一个或多个基因。在一些实施方案中,表1中列出的一个或多个基因包含选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的一个或多个基因。在一些实施方案中,表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的所有9个。在一些实施方案中,表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的所有11个。在一些实施方案中,表1中列出的一个或多个基因包含CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的所有12个。在一些实施方案中,表1中列出的一个或多个基因是表1中列出的所有24个基因。

附图说明

[0025] 图1A是热图,其显示与健康患者对照相比,IRAK4缺陷患者全血中TLR7/8刺激剂R848(瑞喹莫德)对来自GEO登录号GSE25742的微阵列数据集的285个基因(Alsina等人Nat.Immunol.15:1134-42,2014)的诱导显著降低(伪发现率(FDR)<0.05;倍数变化(FC)>1.25)。

[0026] 图1B显示与R848治疗的健康患者对照相比,$IRAK4^{-/-}$和$MyD88^{-/-}$患者中R848(瑞喹莫德)对285个显示诱导显著较低的基因的相对标签得分。

[0027] 图2是热图,其显示与健康患者相比,$IRAK4^{-/-}$患者对R848的反应中未能上调I型IFN和其他TLR调节的基因。

[0028] 图3是一系列图,其显示与相应组的健康患者相比,来自两个肾外组(密歇根大学组和ROSE II期研究组)的系统性红斑狼疮(SLE)患者中已鉴定为差异上调的44个基因中的三个基因(IL1RN、CLEC4E和SMSN1)。$p<0.05$;FC>1.2。

[0029] 图4是一系列图,其显示与IRAK4野生型小鼠相比,IRAK4激酶缺失(IRAK4 kinase-dead)(KD)小鼠的骨髓源巨噬细胞(BMDM)中展示通过R848诱导显著受损的IRAK4通路生物标志物基因(显示CXCL10和CD38)。

[0030] 图5显示与IRAK4野生型小鼠巨噬细胞相比,IRAK4 KD小鼠中R848诱导的IFNβ1表达(extend)显著降低($p=0.02$)。

[0031] 图6是表格,其显示分别与健康和野生型对照相比,人$IRAK4^{-/-}$全血(左列)和IRAK4

KD小鼠巨噬细胞(中列)中R848诱导后的所有24个鉴定的IRAK4通路生物标志物基因及其各自的表达水平。右列显示相对于健康患者对照,SLE患者中每种IRAK4生物标志物的相对表达水平。

[0032] 图7A显示与IRAK4野生型小鼠相比,IRAK4 KD小鼠中R848对IFN调节的基因OAS1A的表达水平的诱导趋向于降低(p＜0.15)。

[0033] 图7B显示与IRAK4野生型小鼠相比,IRAK4 KD小鼠中R848对IFN调节的基因OAS2的表达水平的诱导趋向于降低(p＜0.15)。

[0034] 图7C显示与IRAK4野生型小鼠相比,IRAK4 KD小鼠中R848对IFN调节的基因IFIT1的表达水平的诱导趋向于降低(p＜0.15)。

[0035] 图7D显示与IRAK4野生型小鼠相比,IRAK4 KD小鼠中R848对IFN调节的基因IFNA5的表达水平的诱导趋向于降低(p＜0.15)。

[0036] 图7E显示与IRAK4野生型小鼠相比,IRAK4 KD小鼠中R848对IFN调节的基因MX1的表达水平的诱导趋向于降低(p＜0.15)。

[0037] 图8是表,其显示在人全血样品中使用两种不同的IRAK4小分子抑制剂G03074387(G-4387)(BMS)和G03081557(G-1557)(Pfizer)、用或不用R848刺激的剂量递增的实验结果。在三个测试的人供体样品的至少两个中,将这样的IRAK4生物标志物基因鉴定为“Y”,所述基因显示通过测试IRAK4小分子抑制剂的剂量依赖性下调。

[0038] 图9是一系列图,其显示前9个IRAK4生物标志物基因表达的降低百分比,这些生物标志物基因被两个IRAK4小分子抑制剂G-4387和G-1557剂量依赖性下调。还显示了相应的p值。

[0039] 图10A是热图,其显示表示的12个IRAK4生物标志物基因的相关系数,如从本文所述的ROSE II期研究组的SLE患者血液样品(全血样品)中所测定的。

[0040] 图10B是热图,其显示表示的12个IRAK4生物标志物基因的相关系数,如从本文所述的密歇根大学组的SLE患者血液样品(PBMC样品)中所测定的。

具体实施方式

[0041] I.引言

[0042] 本发明提供了用于治疗白介素-1受体相关激酶4(IRAK4)介导的疾患或病症(例如,免疫疾患(例如,系统性红斑狼疮)或炎性疾患(例如,哮喘)的诊断方法、治疗方法和组合物。本发明至少部分基于以下发现:特定IRAK4通路基因(例如,CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、BCL2A1、CXCL10、CCL8、GPR84、C15orf48、DRAM1、CXCL11、TNFAIP6、CSRNP1、PLSCR1、CLEC4E、SAMSN1和ACSL1)的表达水平可用作生物标志物(例如,预后生物标志物和/或预测生物标志物),用于监测患有IRAK4介导的疾患或病症的患者对包括IRAK4通路抑制剂的治疗的反应的诊断方法、用于鉴定可从包括IRAK4通路抑制剂的治疗中受益的患有IRAK4介导的疾患的患者的方法、以及用于基于一种或多种IRAK4通路基因的表达水平为患有IRAK4介导的疾患或病症的患者选择疗法的方法。还提供了相关的治疗方法和诊断试剂盒。

[0043] II定义

[0044] 应当理解,本文描述的本发明的方面和实施方案包括“包含方面和实施方案”、“由

方面和实施方案组成”和“基本上由方面和实施方案组成”。如本文所用，除非另外指出，否则单数形式“一种(a)”、“一种(an)”和“该”包括复数指代。

[0045] 如本文所用，术语“约”是指本技术领域的技术人员容易知道的各个值的通常误差范围。本文中涉及的“约”某值或参数包括(并描述)针对该值或参数本身的实施方案。例如，涉及“约X”的描述包括“X”的描述。

[0046] 术语“IRAK4通路抑制剂”是指在IRAK4在其中发挥功能的整个通路中降低、阻断、抑制、消除或干扰信号转导的分子。在一些实施方案中，IRAK4通路抑制剂可以抑制参与IRAK4信号传导激活的一种或多种蛋白的活性。在一些实施方案中，IRAK4信号传导抑制剂可以激活参与IRAK4信号传导抑制的一种或多种蛋白的活性。IRAK4通路抑制剂包括但不限于IRAK4抑制剂、IRAK1抑制剂、toll样受体(TLR)抑制剂、白介素-1受体(IL-1R)抑制剂、白介素-33受体(IL-33R)抑制剂、或髓样分化主要反应基因88(MyD88)抑制剂。

[0047] 术语“IRAK4抑制剂”或“IRAK4拮抗剂”是指降低、阻断、抑制、消除或干扰IRAK4激活或功能的分子。在一个具体的实施方案中，IRAK4抑制剂对IRAK4的结合亲和力(解离常数)为约1,000nM或更小。在另一个实施方案中，IRAK4抑制剂对IRAK4的结合亲和力为约100nM或更小。在另一个实施方案中，IRAK4抑制剂对IRAK4的结合亲和力为约50nM或更小。在另一个实施方案中，IRAK4抑制剂对IRAK4的结合亲和力为约10nM或更小。在另一个实施方案中，IRAK4抑制剂对IRAK4的结合亲和力为约1nM或更小。在一个特定的实施方案中，IRAK4抑制剂以1000nM或更小的IC50抑制IRAK4信号传导。在另一个实施方案中，IRAK4抑制剂以500nM或更小的IC50抑制IRAK4信号传导。在另一个实施方案中，IRAK4抑制剂以50nM或更小的IC50抑制IRAK4信号传导。在另一个实施方案中，IRAK4抑制剂以10nM或更小的IC50抑制IRAK4信号传导。在另一个实施方案中，IRAK4抑制剂以1nM或更小的IC50抑制IRAK4信号传导。在一些实施方案中，IRAK4抑制剂是IRAK4的小分子抑制剂。

[0048] 术语“IRAK1抑制剂”或“IRAK1拮抗剂”是指降低、阻断、抑制、消除或干扰IRAK1激活或功能的分子。在一个特定的实施方案中，IRAK1抑制剂对IRAK1的结合亲和力(解离常数)为约1,000nM或更小。在另一个实施方案中，IRAK1抑制剂对IRAK1的结合亲和力为约100nM或更小。在另一个实施方案中，IRAK1抑制剂对IRAK1的结合亲和力为约50nM或更小。在另一个实施方案中，IRAK1抑制剂对IRAK1的结合亲和力为约10nM或更小。在另一个实施方案中，IRAK1抑制剂对IRAK1的结合亲和力为约1nM或更小。在一个特定的实施方案中，IRAK1抑制剂以1000nM或更小的IC50抑制IRAK1信号传导。在另一个实施方案中，IRAK1抑制剂以500nM或更小的IC50抑制IRAK1信号传导。在另一个实施方案中，IRAK1抑制剂以50nM或更小的IC50抑制IRAK1信号传导。在另一个实施方案中，IRAK1抑制剂以10nM或更小的IC50抑制IRAK1信号传导。在另一个实施方案中，IRAK1抑制剂以1nM或更小的IC50抑制IRAK1信号传导。在一些实施方案中，IRAK1抑制剂是IRAK1的小分子抑制剂。

[0049] 术语“toll样受体抑制剂”、“toll样受体拮抗剂”、“TLR抑制剂”或“TLR拮抗剂”是指降低、阻断、抑制、消除或干扰TLR(例如，TLR7、TLR8、TLR9、TLR1、TLR2、TLR4、TLR5、TLR6和/或TLR10)激活或功能的分子。在一个特定的实施方案中，TLR抑制剂对TLR的结合亲和力(解离常数)为约1,000nM或更小。在另一个实施方案中，TLR抑制剂对TLR的结合亲和力为约100nM或更小。在另一个实施方案中，TLR抑制剂对TLR的结合亲和力为约50nM或更小。在另一个实施方案中，TLR抑制剂对TLR的结合亲和力为约10nM或更小。在另一个实施方案中，

TLR抑制剂对TLR的结合亲和力为约1nM或更小。在一个特定的实施方案中,TLR抑制剂以1,000nM或更小的IC50抑制TLR信号传导。在另一个实施方案中,TLR抑制剂以500nM或更小的IC50抑制TLR信号传导。在另一个实施方案中,TLR抑制剂以50nM或更小的IC50抑制TLR信号传导。在另一个实施方案中,TLR抑制剂以10nM或更小的IC50抑制TLR信号传导。在另一个实施方案中,TLR抑制剂以1nM或更小的IC50抑制TLR信号传导。在一些实施方案中,TLR抑制剂是一种或多种TLR的小分子抑制剂。

[0050] 术语“白介素-1受体抑制剂”、“白介素-1受体拮抗剂”、“IL-1R抑制剂”或“IL-1R拮抗剂”是指降低、阻断、抑制、消除或干扰IL-1R激活或功能的分子。在一个特定的实施方案中,IL-1R抑制剂对IL-1R的结合亲和力(解离常数)为约1,000nM或更小。在另一个实施方案中,IL-1R抑制剂对IL-1R的结合亲和力为约100nM或更小。在另一个实施方案中,IL-1R抑制剂对IL-1R的结合亲和力为约50nM或更小。在另一个实施方案中,IL-1R抑制剂对IL-1R的结合亲和力为约10nM或更小。在另一个实施方案中,IL-1R抑制剂对IL-1R的结合亲和力为约1nM或更小。在一个特定的实施方案中,IL-1R抑制剂以1,000nM或更小的IC50抑制IL-1R信号传导。在另一个实施方案中,IL-1R抑制剂以500nM或更小的IC50抑制IL-1R信号传导。在另一个实施方案中,IL-1R抑制剂以50nM或更小的IC50抑制IL-1R信号传导。在另一个实施方案中,IL-1R抑制剂以10nM或更小的IC50抑制IL-1R信号传导。在另一个实施方案中,IL-1R抑制剂以1nM或更小的IC50抑制IL-1R信号传导。在一些实施方案中,IL-1R抑制剂是IL-1R的小分子抑制剂。

[0051] 术语“白介素-33受体抑制剂”、“白介素-33受体拮抗剂”、“IL-33R抑制剂”或“IL-33R拮抗剂”是指降低、阻断、抑制、消除或干扰IL-33R激活或功能的分子。在一个特定的实施方案中,IL-33R抑制剂对IL-33R的结合亲和力(解离常数)为约1000nM或更小。在另一个实施方案中,IL-33R抑制剂对IL-33R的结合亲和力为约100nM或更小。在另一个实施方案中,IL-33R抑制剂对IL-33R的结合亲和力为约50nM或更小。在另一个实施方案中,IL-33R抑制剂对IL-33R的结合亲和力为约10nM或更小。在另一个实施方案中,IL-33R抑制剂对IL-33R的结合亲和力为约1nM或更小。在一个特定的实施方案中,IL-33R抑制剂以1,000nM或更小的IC50抑制IL-33R信号传导。在另一个实施方案中,IL-33R抑制剂以500nM或更小的IC50抑制IL-33R信号传导。在另一个实施方案中,IL-33R抑制剂以50nM或更小的IC50抑制IL-33R信号传导。在另一个实施方案中,IL-33R抑制剂以10nM或更小的IC50抑制IL-33R信号传导。在另一个实施方案中,IL-33R抑制剂以1nM或更小的IC50抑制IL-33R信号传导。在一些实施方案中,IL-33R抑制剂是IL-33R的小分子抑制剂。

[0052] 术语“髓样分化主要反应基因88抑制剂”、“髓样分化主要反应基因88拮抗剂”、“MyD88抑制剂”或“MyD88拮抗剂”是指降低、阻断、抑制、消除或干扰MyD88激活或功能的分子。在一个特定的实施方案中,MyD88抑制剂对MyD88的结合亲和力(解离常数)为约1,000nM或更小。在另一个实施方案中,MyD88抑制剂对MyD88的结合亲和力为约100nM或更小。在另一个实施方案中,MyD88抑制剂对MyD88的结合亲和力为约50nM或更小。在另一个实施方案中,MyD88抑制剂对MyD88的结合亲和力为约10nM或更小。在另一个实施方案中,MyD88抑制剂对MyD88的结合亲和力为约1nM或更小。在一个特定的实施方案中,MyD88抑制剂以1000nM或更小的IC50抑制MyD88信号传导。在另一个实施方案中,MyD88抑制剂以500nM或更小的IC50抑制MyD88信号传导。在另一个实施方案中,MyD88抑制剂以50nM或更小的IC50抑制

MyD88信号传导。在另一个实施方案中,MyD88抑制剂以10nM或更小的IC50抑制MyD88信号传导。在另一个实施方案中,MyD88抑制剂以1nM或更小的IC50抑制MyD88信号传导。在一些实施方案中,MyD88抑制剂是MyD88的小分子抑制剂。

[0053] 术语“CD38”是指分化簇38,并且包括其同源物、突变和同种型。CD38在本领域中也称为ADPRC1。该术语包括未加工的全长CD38,以及在细胞中加工产生的任何形式的CD38。该术语包括CD38的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人CD38的CD38基因、mRNA序列(例如,SEQ ID NO:1;GenBank登录号NM_001775.3)和人CD38的氨基酸序列(例如,SEQ ID NO:2;UniProtKB登录号P28907)以及来自任何其他脊椎动物来源的CD38 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0054] 术语“SOCS3”是指细胞因子信号传导3的抑制剂,并且包括其同源物、突变和同种型。SOCS3在本领域中也称为细胞因子诱导的SH2蛋白3(CIS3)、STAT诱导的STAT抑制剂3(SSI3)和ATOD4。该术语包括未加工的全长SOCS3,以及在细胞中加工产生的任何形式的SOCS3。该术语包括SOCS3的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人SOCS3的SOCS3基因、mRNA序列(例如,SEQ ID NO:3;GenBank登录号NM_003955.4)和人SOCS3的氨基酸序列(例如,SEQ ID NO:4;UniProtKB登录号O14543)以及来自任何其他脊椎动物来源的SOCS3 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0055] 术语“AQP9”是指水通道蛋白9,并且包括其同源物、突变和同种型。在本领域中,AQP9也称为水甘油通道蛋白9、HsT17287、T17287和小溶质通道1(SSC1)。该术语包括未加工的全长AQP9,以及在细胞中加工产生的任何形式的AQP9。该术语包括AQP9的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人AQP9的AQP9基因、mRNA序列(例如,SEQ ID NO:5;GenBank登录号NM_020980.4)和人AQP9的氨基酸序列(例如,SEQ ID NO:6;UniProtKB登录号O43315)以及来自任何其他脊椎动物来源的AQP9 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0056] 术语“CDKN1A”是指细胞周期蛋白依赖性激酶抑制剂1A,并且包括其同源物、突变和同种型。CDKN1A在本领域中也称为CDK相互作用蛋白1(CIP1)、黑素瘤分化相关蛋白6(MDA-6)或野生型P53激活片段1(WAF-1)。该术语包括未加工的全长CDKN1A,以及在细胞中加工产生的任何形式的CDKN1A。该术语包括CDKN1A的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人CDKN1A的CDKN1A基因、mRNA序列(例如SEQ ID NO:7;GenBank登录号NM_000389)和人CDKN1A的氨基酸序列(例如SEQ ID NO:8;UniProtKB登录号P38936)以及来自任何其他脊椎动物来源的CDKN1A DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如小鼠和大鼠)。

[0057] 术语“GADD45B”是指生长停滞和DNA损伤诱导型Beta,并且包括其同源物、突变及其同种型。GADD45B在本领域中也称为髓样分化初级反应蛋白MyD118(MYD118)。该术语包括未加工的全长GADD45B,以及在细胞中加工产生的任何形式的GADD45B。该术语包括GADD45B的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人GADD45B的GADD45B基因、mRNA序列(例如,SEQ ID NO:9;GenBank登录号NM_015675)和人GADD45B的氨基酸序列(例如,SEQ ID NO:10;和UniProtKB登录号O75293)以及来自任何其他脊椎动物来源的GADD45B DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大

鼠)。

[0058] 术语“B4GALT5”是指β-1,4-半乳糖基转移酶5,并包括其同源物、突变和同种型。B4GALT5在本领域中也称为UDP-半乳糖:β-N-乙酰基葡糖胺。该术语包括未加工的全长B4GALT5,以及在细胞中加工产生的任何形式的B4GALT5。该术语包括B4GALT5的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人B4GALT5的B4GALT5基因、mRNA序列(例如SEQ ID NO:11;GenBank登录号NM_004776),以及人B4GALT5的氨基酸序列(例如SEQ ID NO:12;UniProtKB登录号043286)以及来自任何其他脊椎动物来源的B4GALT5 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如小鼠和大鼠)。

[0059] 术语“IL15RA”是指白介素-15受体亚基α,并且包括其同源物、突变和同种型。IL15RA在本领域中也称为CD215。该术语包括未加工的全长IL15RA,以及在细胞中加工产生的任何形式的IL15RA。该术语包括IL15RA的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人IL15RA的IL15RA基因、mRNA序列(例如,SEQ ID NO:13;GenBank登录号NM_008358)和人IL15RA的氨基酸序列(例如,SEQ ID NO:14;UniProtKB登录号Q13261)以及来自任何其他脊椎动物来源的IL15RA DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0060] 术语“TNFAIP3”是指TNFα诱导的蛋白3,并且包括其同源物、突变和同种型。TNFAIP3在本领域中也称为A20、OTUD7C或AISBL。该术语包括未加工的全长TNFAIP3,以及在细胞中加工产生的任何形式的TNFAIP3。该术语包括TNFAIP3的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人TNFAIP3的TNFAIP3基因、mRNA序列(例如,SEQ ID NO:15;GenBank登录号NM_001270508)和人TNFAIP3的氨基酸序列(例如,SEQ ID NO:16;UniProtKB登录号P21580)以及来自任何其他脊椎动物来源的TNFAIP3 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0061] 术语“SOCS1”是指细胞因子信号传导1的抑制剂,并且包括其同源物、突变和同种型。SOCS1在本领域中也称为STAT诱导的STAT抑制剂1(SSI1)、Tec相互作用蛋白3(TIP3)、细胞因子诱导的SH2蛋白1(CISH1)或JAK结合蛋白。该术语包括未加工的全长SOCS1以及在细胞中加工产生的任何形式的SOCS1。该术语包括SOCS1的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人SOCS1的SOCS1基因、mRNA序列(例如,SEQ ID NO:17;GenBank登录号NM_003745)和人SOCS1的氨基酸序列(例如,SEQ ID NO:18;UniProtKB登录号015524)以及来自任何其他脊椎动物来源的SOCS1DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0062] 术语“IL1RN”是指白介素1受体拮抗剂,并且包括其同源物、突变和同种型。IL1RN在本领域中也称为Anakinra、IRAP、DIRA或MVCD4。该术语包括未加工的全长IL1RN,以及在细胞中加工产生的任何形式的IL1RN。该术语包括IL1RN的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人IL1RN的IL1RN基因、mRNA序列(例如,SEQ ID NO:19;GenBank登录号NM_173842)和人IL1RN的氨基酸序列(例如,SEQ ID NO:20;UniProtKB登录号P18510)以及来自任何其他脊椎动物来源的IL1RN DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0063] 术语“PFKFB3”是指6-磷酸果糖-2-激酶/果糖-2,6-二磷酸酶3,并且包括其同源物、突变和同种型。PFKFB3在本领域中也称为IPFK2、PFK2或iPFK-2。该术语包括未加工的全

长PFKFB3,以及在细胞中加工产生的任何形式的PFKFB3。该术语包括PFKFB3的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人PFKFB3的PFKFB3基因、mRNA序列(例如SEQ ID NO:21;GenBank登录号NM_004566)和人PFKFB3的氨基酸序列(例如SEQ ID NO:22;UniProtKB登录号Q16875)以及来自任何其他脊椎动物来源的PFKFB3 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如小鼠和大鼠)。

[0064] 术语"BCL2A1"是指BCL2相关蛋白A1,并且包括其同源物、突变和同种型。BCL2A1在本领域中也称为GRS、ACC1、ACC2、BFL1、ACC-1、ACC-2、HBPA1或BCL2L5。该术语包括未加工的全长BCL2A1,以及在细胞中加工产生的任何形式的BCL2A1。该术语包括BCL2A1的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人BCL2A1的BCL2A1基因、mRNA序列(例如,SEQ ID NO:23;GenBank登录号NM_004049)以及人BCL2A1的氨基酸序列(例如,SEQ ID NO:24;UniProtKB登录号Q16548)以及来自任何其他脊椎动物来源的BCL2A1 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0065] 术语"CXCL10"是指C-X-C基序趋化因子配体10,并且包括其同源物、突变和同种型。CXCL10在本领域中也称为C7、IFI10、INP10、IP-10、crg-2、mob-1、SCYB10或gIP-10。该术语包括未加工的全长CXCL10,以及在细胞中加工产生的任何形式的CXCL10。该术语包括CXCL10的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如,人CXCL10的CXCL10基因、mRNA序列(例如,SEQ ID NO:25;GenBank登录号NM_001565)和人CXCL10的氨基酸序列(例如,SEQ ID NO:26;UniProtKB登录号P02778)以及来自任何其他脊椎动物来源的CXCL10 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如小鼠和大鼠)。

[0066] 术语"CCL8"是指C-C基序趋化因子配体8,并且包括其同源物、突变和同种型。CCL8在本领域中也称为HC14、MCP2、MCP-2、SCYA8或SCYA10。该术语包括未加工的全长CCL8,以及在细胞中加工产生的任何形式的CCL8。该术语包括CCL8的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人CCL8的CCL8基因、mRNA序列(例如,SEQ ID NO:27;GenBank登录号NM_005623)和人CCL8的氨基酸序列(例如,SEQ ID NO:28;UniProtKB登录号P80075)以及来自任何其他脊椎动物来源的CCL8 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0067] 术语"GPR84"是指G蛋白偶联受体84,并且包括其同源物、突变和同种型。GPR84在本领域中也称为EX33或GPCR4。该术语包括未加工的全长GPR84,以及在细胞中加工产生的任何形式的GPR84。该术语包括GPR84的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人GPR84的GPR84基因、mRNA序列(例如,SEQ ID NO:29;GenBank登录号NM_020370),以及人GPR84的氨基酸序列(例如,SEQ ID NO:30;UniProtKB登录号Q9NQS5)以及来自任何其他脊椎动物来源的GPR84 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0068] 术语"C15orf48"是指15号染色体开放阅读框48,并且包括其同源物、突变和同种型。C15orf48在本领域中也称为NMES1或FOAP-11。该术语包括未加工的全长C15orf48,以及在细胞中加工产生的任何形式的C15orf48。该术语包括C15orf48的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人C15orf48的C15orf48基因、mRNA序列(例如,SEQ ID NO:31;GenBank登录号NM_197955)和人C15orf48的氨基酸序列(例如,SEQ ID NO:

32;UniProtKB登录号Q9C002)以及任何其他脊椎动物来源的C15orf48 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如小鼠和大鼠)。

[0069] 术语“DRAM1”是指DNA损伤调节的自噬调节剂1,并且包括其同源物、突变和同种型。DRAM1在本领域中也称为DRAM。该术语包括未加工的全长DRAM1,以及在细胞中加工产生的任何形式的DRAM1。该术语包括DRAM1的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人DRAM1的DRAM1基因、mRNA序列(例如,SEQ ID NO:33;GenBank登录号NM_018370)以及人DRAM1的氨基酸序列(例如,SEQ ID NO:34;UniProtKB登录号Q8N682)以及来自任何其他脊椎动物来源的DRAM1 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0070] 术语“CXCL11”是指C-X-C基序趋化因子配体11,并且包括其同源物、突变和同种型。CXCL11在本领域中也称为IP9、H174、IP-9、b-R1、I-TAC、SCYB11或SCYB9B。该术语包括未加工的全长CXCL11以及在细胞中加工产生的任何形式的CXCL11。该术语包括CXCL11的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人CXCL11的CXCL11基因、mRNA序列(例如,SEQ ID NO:35;GenBank登录号NM_005409)和人CXCL11的氨基酸序列(例如,SEQ ID NO:36;UniProtKB登录号O14625)以及来自任何其他脊椎动物来源的CXCL11 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0071] 术语“TNFAIP6”是指TNFα诱导的蛋白6,并且包括其同源物、突变和同种型。TNFAIP6在本领域中也称为TSG6或TSG-6。该术语包括未加工的全长TNFAIP6,以及在细胞中加工产生的任何形式的TNFAIP6。该术语包括TNFAIP6的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人TNFAIP6的TNFAIP6基因、mRNA序列(例如,SEQ ID NO:37;GenBank登录号NM_007115)和人TNFAIP6的氨基酸序列(例如,SEQ ID NO:38;UniProtKB登录号P98066)以及来自任何其他脊椎动物来源的TNFAIP6 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0072] 术语“CSRNP1”是指富含半胱氨酸和丝氨酸的核蛋白1,并且包括其同源物、突变和同种型。CSRNP1在本领域中也称为AXUD1、URAX1、TAIP-3、CSRNP-1或FAM130B。该术语包括未加工的全长CSRNP1,以及在细胞中加工产生的任何形式的CSRNP1。该术语包括CSRNP1的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人CSRNP1的CSRNP1基因、mRNA序列(例如,SEQ ID NO:39;GenBank登录号NM_033027)和人CSRNP1的氨基酸序列(例如,SEQ ID NO:40;UniProtKB登录号Q96S65)以及来自任何其他脊椎动物来源的CSRNP1 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0073] 术语“PLSCR1”是指磷脂加扰酶(scramblase)1,并且包括其同源物、突变和同种型。PLSCR1在本领域中也称为MMTRA1B。该术语包括未加工的全长PLSCR1,以及在细胞中加工导致的任何形式的PLSCR1。该术语包括PLSCR1的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人PLSCR1的PLSCR1基因、mRNA序列(例如,SEQ ID NO:41;GenBank登录号NM_021105)和人PLSCR1的氨基酸序列(例如,SEQ ID NO:42;UniProtKB登录号O15162)以及来自任何其他脊椎动物来源的PLSCR1 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0074] 术语“CLEC4E”是指C型凝集素结构域家族4成员E,并且包括其同源物、突变和同种型。CLEC4E在本领域中也称为MINCLE或CLECSF9。该术语包括未加工的全长CLEC4E,以及在

细胞中加工产生的任何形式的CLEC4E。该术语包括CLEC4E的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人CLEC4E的CLEC4E基因、mRNA序列(例如,SEQ ID NO:43;GenBank登录号NM_014358)和人CLEC4E的氨基酸序列(例如,SEQ ID NO:44;UniProtKB登录号Q9ULY5)以及来自任何其他脊椎动物来源的CLEC4E DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0075] 术语“SAMSN1”是指SAM结构域、SH3结构域和核定位信号1,并且包括其同源物、突变和同种型。SAMSN1在本领域中也称为SLy2、HACS1、NASH1、SASH2或SH3D6B。该术语包括未加工的全长SAMSN1,以及在细胞中加工产生的任何形式的SAMSN1。该术语包括SAMSN1的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人SAMSN1的SAMSN1基因、mRNA序列(例如,SEQ ID NO:45;GenBank登录号NM_022136)和人SAMSN1的氨基酸序列(例如,SEQ ID NO:46;UniProtKB登录号Q9NSI8)以及来自任何其他脊椎动物来源的SAMSN1 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0076] 术语“ACSL1”是指酰基辅酶A合成酶长链家族成员1,并且包括其同源物、突变及其同种型。ACSL1在本领域中也称为Acs、Acas、FACS、Acasl、Facl2或LACS1。该术语包括未加工的全长ACSL1,以及在细胞中加工产生的任何形式的ACSLI。该术语包括ACSL1的天然存在的变体(例如剪接变体或等位基因变体)。该术语包括例如人ACSL1的ACSLI基因、mRNA序列(例如,SEQ ID NO:47;GenBank登录号NM_001286708)和人ACSL1的氨基酸序列(例如,SEQ ID NO:48;UniProtKB登录号P33121)以及来自任何其他脊椎动物来源的ACSL1 DNA、mRNA和氨基酸序列,包括哺乳动物,如灵长动物和啮齿动物(例如,小鼠和大鼠)。

[0077] 如本文所用,术语“患者”、“个体”和“受试者”可互换使用,是指希望治疗的任何单个动物,更优选哺乳动物(包括如非人动物,例如猫、狗、马、兔子、动物园动物、牛、猪、绵羊和非人灵长动物)。在特定的实施方案中,本文的患者是人。该患者可以是患有、怀疑患有、或有风险患有IRAK4介导的疾患或病症(例如,免疫疾患、炎性疾患、纤维化疾患、嗜酸性细胞疾患、感染、疼痛、中枢神经系统疾患、急性肾脏损伤、慢性肾脏疾病、子宫内膜异位症、非酒精性脂肪肝疾病、代谢综合征和肥胖症)。患者可能先前已用IRAK4通路抑制剂、其他药物治疗或之前未进行过治疗。开始治疗时,患者可能对其他使用的药物是“首次用于实验的”,也就是说,患者可能先前在“基线”(即在施用本文治疗方法中的第一剂量的IRAK4通路抑制剂之前的设定时间点,如在治疗开始前筛选受试者的日子)时未接受过除包括“IRAK4通路抑制剂”的疗法以外的其他疗法。通常认为这种“首次用于实验的”患者或受试者是用此类其他药物治疗的候选者。

[0078] 本文中的术语“抗体”以最广义使用,并且包括各种抗体结构,包括但不限于单克隆抗体、多克隆抗体、多特异性抗体(例如,双特异性抗体)和抗体片段,只要它们表现出期望的抗原结合活性。

[0079] 本文可互换使用的“多核苷酸”或“核酸”是指任何长度的核苷酸的聚合物,包括DNA和RNA。核苷酸可以是脱氧核糖核苷酸、核糖核苷酸、修饰的核苷酸或碱基和/或其类似物,或可以通过DNA或RNA聚合酶或通过合成反应并入聚合物中的任何底物。因此,例如,本文所定义的多核苷酸包括但不限于单链和双链DNA、包括单链和双链区域的DNA、单链和双链RNA以及包括单链和双链区域的RNA、包含DNA和RNA的杂合分子,其可以是单链的,或更典型地是双链的或包含单链和双链的区域。另外,本文所用的术语“多核苷酸”还指包含RNA或

DNA或RNA和DNA两者的三链区域。在这些区域中的链可以来自相同分子或不同分子。该区域可以包括一个或多个分子的全部，但是更典型地仅包括一些分子的区域。三螺旋区的分子之一通常是寡核苷酸。术语“多核苷酸”具体包括cDNA。

[0080] 多核苷酸可以包含修饰的核苷酸，如甲基化的核苷酸及其类似物。如果存在对核苷酸结构的修饰，其可以在聚合物组装之前或之后进行。核苷酸的序列可以被非核苷酸组分中断。多核苷酸可在合成后被进一步修饰，如通过与标签缀合。其他类型的修饰包括，例如“帽”，用类似物取代一个或多个天然存在的核苷酸、核苷酸间修饰，例如用不带电荷的键(例如，膦酸甲酯、磷酸三酯、氨基磷酸酯、氨基甲酸酯等)和带电荷的键(例如，硫代磷酸酯、二硫代磷酸酯等)的那些修饰、含有悬挂部分例如蛋白质(例如，核酸酶、毒素、抗体、信号肽、聚-L-赖氨酸等)的那些修饰、带嵌入剂(如吖啶、补骨脂素等)的那些修饰、含有螯合剂(例如金属、放射性金属、硼、氧化性金属等)的那些修饰、含有烷化剂的那些修饰、具有修饰的键的那些修饰(例如，α异头核酸)以及未修饰形式的多核苷酸。此外，糖中通常存在的任何羟基可以被例如膦酸酯基团、磷酸基团取代，被标准保护基团保护，或者被激活以制备与其他核苷酸的其他键，或者可以与固体或半固体支持物缀合。5’和3’末端OH可以被磷酸化或被胺或1至20个碳原子的有机封端基部分取代。其他羟基也可以被衍生为标准保护基。多核苷酸还可以包含本领域通常已知的核糖或脱氧核糖的类似物形式，包括例如2’-O-甲基-、2’-O-烯丙基-、2’-氟-或2’-叠氮核糖、碳环糖类似物、α-异头糖、差向异构糖，如阿拉伯糖、木糖或来苏糖、吡喃糖、呋喃糖、景天庚酮糖、无环类似物和无碱基核苷类似物，如甲基核糖苷。一个或多个磷酸二酯键可以被替代的连接基团取代。这些替代的连接基团包括但不限于以下实施方案，其中磷酸酯被P(O)S(“硫代酸酯”)、P(S)S(“二硫代酸酯”)、(O)NR_2(“酰胺酸酯”)、P(O)R、P(O)OR’、CO或CH_2(“甲缩醛(formacetal)”)取代，其中每个R或R’独立地为H或取代或未取代的烷基(1-20C)，可选地包含醚(-O-)键、芳基、烯基、环烷基、环烯基或芳烷基(araldyl)。并非多核苷酸中的所有键都需要相同。多核苷酸可包含一种或多种不同类型的本文所述的修饰和/或多种相同类型的修饰。先前的描述适用于本文所指的所有多核苷酸，包括RNA和DNA。

[0081] 如本文所用，“寡核苷酸”通常是指短的单链多核苷酸，其长度(但非必须)小于约250个核苷酸。寡核苷酸可以是合成的。术语“寡核苷酸”和“多核苷酸”不是互相排斥的。上面对多核苷酸的描述同样且完全适用于寡核苷酸。

[0082] 术语“引物”是指单链多核苷酸，其能够与核酸杂交并通常通过提供游离的3’-OH基团允许互补核酸聚合。

[0083] 术语“小分子”是指分子量为约2000道尔顿或更小，优选地为约500道尔顿或更小的任何分子。

[0084] 术语“检测”包括任何检测手段，包括直接和间接检测。

[0085] 如本文所用，术语“生物标志物”是指可以在样品中被检测到的指示分子或分子组(例如，预测、诊断和/或预后指示)，包括例如CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、BCL2A1、CXCL10、CCL8、GPR84、C15orf48、DRAM1、CXCL11、TNFAIP6、CSRNP1、PLSCR1、CLEC4E、SAMSN1和ACSL1。生物标志物可以是预测生物标志物，并用作患有特定疾患或病症(例如IRAK4介导的疾患或病症)的患者对IRAK4通路抑制剂治疗敏感或受益的可能性的指示。生物标志物包括但不限于多核苷酸(例如DNA和/或RNA

(例如mRNA))、多核苷酸拷贝数改变(例如DNA拷贝数)、多肽、多肽和多核苷酸修饰(例如翻译后修饰)、碳水化合物和/或基于糖脂分子的标记。在一些实施方案中,生物标志物是基因。

[0086] 如本文所用,生物标志物的“量”或“水平”是生物样品中可检测的水平。这些可以通过本领域技术人员已知并且在本文中公开的方法来测量。

[0087] 术语“表达水平”或“表达的水平”通常是指生物样品中生物标志物的量。“表达”通常是指将信息(例如,基因编码和/或外遗传基因信息)转化为细胞中存在并运行的结构的过程。因此,如本文所用,“表达”可以指转录成多核苷酸、翻译成多肽、或者甚至是多核苷酸和/或多肽修饰(例如,多肽的翻译后修饰)。转录的多核苷酸、翻译的多肽或多核苷酸和/或多肽修饰(例如,多肽的翻译后修饰)的片段也应被视为表达,无论它们是源自选择性剪接生成的转录本或降解的转录本、还是源自多肽的翻译后加工(例如,通过蛋白水解)。“表达的基因”包括被转录成mRNA多核苷酸然后被翻译成多肽的那些基因,以及被转录成RNA但未被翻译成多肽的那些基因(例如,转运和核糖体RNA)。

[0088] “增加的表达”、“增加的表达水平”、“增加的水平”、“提高的表达”、“提高的表达水平”或“提高的水平”是指相对于对照,个体中生物标志物增加的表达或增加的水平,所述对照如没有疾患或病症(例如IRAK4介导的疾患或病症)的一个或多个个体(例如健康个体)、内部对照(例如管家生物标志物)或来自患者组/群的样品中生物标志物的中位表达水平。

[0089] “减小的表达”、“减小的表达水平”、“减小的水平”、“降低的表达”、“降低的表达水平”或“降低的水平”是指相对于对照个体中生物标志物的减小的表达或减小的水平,所述对照如没有疾患或病症(例如IRAK4介导的疾患或病症)的一个或多个个体(例如健康个体)、内部对照(例如管家生物标志物)或来自患者组/群的样品中生物标志物的中位表达水平。在一些实施方案中,降低的表达是几乎没有或没有表达。

[0090] 术语“管家基因”在本文中是指编码蛋白质的基因或基因组,其活性对于维持细胞功能是必不可少的,并且通常在所有细胞类型中类似地存在。

[0091] 如本文所用,“扩增”通常是指产生所需序列的多个拷贝的方法。“多个拷贝”是指至少两个拷贝。“拷贝”不一定意味着与模板序列完全序列互补或相同。例如,拷贝可以包括核苷酸类似物,如脱氧肌苷、有意的序列改变(如通过包含可与模板杂交但不互补的序列的引物引入的序列改变)、和/或在扩增过程中发生的序列错误。

[0092] 如本文所用,“聚合酶链反应”或“PCR”技术通常是指这样的程序,其中微量的核酸、RNA和/或DNA的特定片段如例如美国专利No.4,683,195中所述扩增。通常,需要从感兴趣区域的末端或以外获得序列信息,以便可以设计寡核苷酸引物。这些引物在序列上与待扩增模板的相反链相同或相似。两条引物的5’末端核苷酸可以与扩增材料的末端一致。PCR可用于扩增来自总基因组DNA的特定RNA序列、特定DNA序列、以及从总细胞RNA、噬菌体或质粒序列等转录的cDNA。通常参见Mullis等人,Cold Spring Harbor Symp.Quant.Biol.51:263(1987)和Erlich,编辑,PCR Technology,(Stockton Press,NY,1989)。如本文所用,PCR被认为是用于扩增核酸测试样品的核酸聚合酶反应方法中的一种,但不是唯一的实例,所述方法包括使用已知的核酸(DNA或RNA)作为引物并利用核酸聚合酶来扩增或产生特定核酸片段或扩增或产生与特定核酸互补的特定核酸片段。

[0093] “定量聚合酶链反应”或“qPCR”是指一种PCR形式,其中在PCR反应的每个步骤中测

量PCR产物的量。该技术已经在各种出版物中进行了描述，包括例如Cronin等人，Am.J.Pathol.164(1):35-42(2004)和Ma等人,Cancer Cell 5:607-616(2004)。

[0094] 术语“微阵列”是指可杂交的阵列元件，优选多核苷酸探针，在底物上的有序排列。

[0095] 如本文所用，术语“样品”是指获自或衍生自受试者(例如，感兴趣个体)的组合物，其包含例如基于物理、生化、化学和/或生理特征待表征和/或鉴定的细胞和/或其他分子实体。例如，短语“疾病样品”及其变体是指从感兴趣的受试者获得的任何样品，其预期或已知包含待表征的细胞和/或分子实体。样品包括但不限于组织样品、原代或培养细胞或细胞系、细胞上清液、细胞裂解物、血小板、血清、血浆、玻璃体液、淋巴液、滑液、卵泡液、精液、羊水、乳、全血、血液来源的细胞、尿液、脑脊液、唾液、痰、泪液、汗液、粘液、肿瘤溶解物和组织培养基、组织提取物(如匀浆组织、肿瘤组织、细胞提取物及其组合)。

[0096] “组织样品”或“细胞样品”是指从受试者或个体的组织获得的相似细胞的集合。组织或细胞样品的来源可以是来自新鲜、冷冻和/或保存的器官、组织样品、活检和/或抽吸的实体组织；血液或任何血液成分，如血浆；体液，如脑脊髓液、羊水、腹膜液或间质液；受试者妊娠或发育中任何时期的细胞。组织样品也可以是原代或培养的细胞或细胞系。任选地，组织或细胞样品获自疾病组织/器官。例如，肿瘤样品是从肿瘤或其他癌组织获得的组织样品。

[0097] 如本文所用，“参考样品”、“参考细胞”、“参考组织”、“对照样品”、“对照细胞”或“对照组织”是指用于比较目的的样品、细胞、组织、标准或水平。在一个实施方案中，参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织获自相同受试者或个体的身体的健康和/或未患病部位(例如，组织或细胞)。例如，参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织可以是与患病细胞或组织相邻的健康的和/或未患病的细胞或组织。在另一个实施方案中，参考样品获自相同受试者或个体身体的未经处理的组织和/或细胞。在又一个实施方案中，参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织获自不是受试者或个体的个体的身体的健康和/或未患病的部位(例如，组织或细胞)。在另一个实施方案中，参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织获自不是受试者或个体的个体的身体的未经处理的组织和/或细胞。

[0098] 为了本文的目的，组织样品的“部分”是指组织样品的单个部分或片，例如，从组织样品切下的组织或细胞的薄切片。应当理解，可以获取组织样品的多个部分并进行分析，条件是应理解，可以在形态学和分子水平上分析组织样品的相同部分，或者对多肽(例如，通过免疫组织化学)和/或多核苷酸(例如通过原位杂交)进行分析。

[0099] “相关联”或“相关的”意味着以任何方式将第一分析或方案的性能和/或结果与第二分析或方案的性能和/或结果进行比较。例如，可以使用第一分析或方案的结果进行第二方案，和/或可以使用第一分析或方案的结果来确定是否应该进行第二分析或方案。关于多肽分析或方案的实施方案，可以使用多肽表达分析或方案的结果来确定是否应进行特定的治疗方案。关于多核苷酸分析或方案的实施方案，可以使用多核苷酸表达分析或方案的结果来确定是否应进行特定的治疗方案。

[0100] 可以使用表明对个体有益的任何终点来评估“个体反应”或“反应”，包括但不限于(1)在一定程度上抑制IRAK4介导的疾患或病症的进展，包括减慢或完全缓解；(2)在一定程

度上缓解与IRAK4介导的疾患或病症相关的一个或多个症状;(6)增加或延长存活,包括总体存活和无进展存活;和/或(7)在治疗后的给定时间点降低死亡率。

[0101] 术语“存活”是指患者还活着,并且包括总体存活以及无进展存活。

[0102] 如本文所用,“无进展存活”或“PFS”是指在治疗期间和之后所治疗的疾病(例如IRAK4介导的疾患或病症(例如免疫疾患(例如系统性红斑狼疮(SLE))或炎性疾患(例如哮喘))没有进展或恶化的时间长度。无进展存活可以包括个体经历完全反应或部分反应的时间,以及个体经历稳定疾病的时间。

[0103] 如本文所用,“总体存活”或“OS”是指在特定时间期间(例如从诊断或治疗时开始的6个月、1年、2年、3年、4年、5年、10年、15年、20年或超过20年)之后一组中可能存活的受试者百分比。

[0104] 对药物治疗的患者的“有效反应”或患者的“反应性”以及类似措词是指赋予患者的临床或治疗益处,所述患者有风险患有或患有IRAK4介导的疾患或病症,如免疫疾患(例如系统性红斑狼疮(SLE))或炎性疾患(例如哮喘)。在一个实施方案中,表1中列出的一个或多个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)用于鉴定相对于不表达表1中列出的一个或多个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)的患者,预测对药物治疗(例如,包括IRAK4通路抑制剂的治疗)有增加的反应可能性的患者。在一个实施方案中,表1中列出的一个或多个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)用于鉴定相对于不以相同的水平表达表1中列出的一个或多个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)的患者,预测对药物治疗(例如,包括IRAK4通路抑制剂的治疗)有增加的反应可能性的患者。

[0105] “疾患”是将从治疗中受益的任何病症,包括但不限于慢性和急性疾患或疾病,包括使哺乳动物易患所讨论的病患的那些病理病症。

[0106] 术语“药物制剂”是指这样的制剂,其形式允许其中所包含的活性成分的生物活性有效的,并且不包含对施用该制剂的受试者具有不可接受的毒性的其他组分。

[0107] “可药用赋形剂”是指药物制剂中除活性成分以外的对受试者无毒的成分。可药用赋形剂包括但不限于缓冲剂、载体、稳定剂或防腐剂。

[0108] 术语“可药用盐”表示不是生物学上或其他方面不希望的盐。可药用盐包括酸和碱加成盐。短语“可药用”表示该物质或组合物必须与形成制剂的其他成分和/或用其治疗的哺乳动物在化学和/或毒理学上相容。

[0109] 术语“可药用酸加成盐”是指与无机酸和有机酸形成的那些可药用盐,所述无机酸如盐酸、氢溴酸、硫酸、硝酸、碳酸、磷酸,所述有机酸选自脂族、脂环族、芳族、芳脂族、杂环、羧酸和磺酸类有机酸,如甲酸、乙酸、丙酸、乙醇酸、葡萄糖酸、乳酸、丙酮酸、草酸、苹果酸、马来酸、丙二酸、琥珀酸、富马酸、酒石酸、柠檬酸、天冬氨酸、抗坏血酸、谷氨酸、邻氨基苯甲酸、苯甲酸、肉桂酸、扁桃酸、双羟萘酸、苯乙酸、甲磺酸“甲磺酸酯”、乙磺酸、对甲苯磺酸和水杨酸。

[0110] 术语“可药用碱加成盐”表示与有机或无机碱形成的那些可药用盐。可接受的无机碱的实例包括钠、钾、铵、钙、镁、铁、锌、铜、锰和铝盐。衍生自可药用有机无毒碱的盐包括伯

胺、仲胺和叔胺、取代胺(包括天然存在的取代胺)、环胺的盐和碱性离子交换树脂的盐,如异丙胺、三甲胺、二乙胺、三乙胺、三丙胺、乙醇胺、2-二乙基氨基乙醇、三甲胺、二环己胺、赖氨酸、精氨酸、组氨酸、咖啡因、普鲁卡因、海巴明、胆碱、甜菜碱、乙二胺、葡糖胺、甲基葡糖胺、可可碱、嘌呤、哌嗪、哌啶、N-乙基哌啶和多胺树脂的盐。

[0111] 如本文所用,“治疗”(及其语法变化,如“治”或“治疗”)是指试图改变被治疗个体的自然病程的临床干预,并且可以用于进行预防或在临床病理过程中进行。理想的治疗效果包括但不限于预防疾病的发生或复发、减轻症状、减低疾患的任何直接或间接病理后果、预防转移、降低疾病进展的速度、缓解或减轻疾病状态、和缓解或预后改善。在一些实施方案中,IRAK4通路抑制剂(例如IRAK4抑制剂、IRAK1抑制剂、toll样受体(TLR)抑制剂、白介素-1受体(IL-1R)抑制剂、白介素-33受体(IL-33R)抑制剂或髓样分化主要反应基因88(MyD88)抑制剂)可用于延迟IRAK4介导的疾患或病症的发展或减缓IRAK4介导的疾患或病症的进展。

[0112] 如本文所用,“施用”是指给予受试者(例如患者)某一剂量化合物(例如,IRAK4通路抑制剂,如IRAK4抑制剂或拮抗剂)或药物组合物(例如,包含抑制剂或拮抗剂的药物组合物)的方法。可以通过任何合适的方式进行施用,包括肠胃外、肺内和鼻内施用,如果需要用于局部治疗,则可以病灶内施用。肠胃外输注包括例如肌内、静脉内、动脉内、腹膜内或皮下施用。可以通过任何合适的途径进行给药,例如通过注射,如静脉内或皮下注射,部分取决于施用是短暂的还是长期的。本文考虑了各种给药方案,包括但不限于单次或在不同时间点上的多次施用、推注施用和脉冲输注。

[0113] 本文使用的术语“共同施用”是指两种或更多种治疗剂的施用,其中至少部分施用在时间上重叠。因此,同时施用包括在停止一种或多种其他药剂的施用之后继续一种或多种药剂的施用时的给药方案。

[0114] “降低或抑制”是指引起总体下降10%、20%、30%、40%、50%、60%、70%、75%、80%、85%、90%、95%或更多的能力。降低或抑制可以指例如IRAK4通路中蛋白质的活性和/或功能水平(例如,通过IRAK4通路的信号转导水平)的降低或抑制。另外,降低或抑制可以指例如所治疗疾患或病症的症状(例如,IRAK4介导的疾患或病症)的降低或抑制。

[0115] 术语“包装插页”用于指通常包含在治疗产品的商业包装中的说明书,该说明书包含有关使用此类治疗产品的适应症、用法、剂量、施用、组合治疗、禁忌症和/或警告的信息。

[0116] “制品”是任何产品(例如,包装或容器)或试剂盒,其包含至少一种试剂,例如用于治疗疾患或病症(例如,IRAK4介导的疾患或病症)的药物或用于特异性检测本文所述的生物标志物(例如CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、BCL2A1、CXCL10、CCL8、GPR84、C15orf48、DRAM1、CXCL11、TNFAIP6、CSRNP1、PLSCR1、CLEC4E、SAMSN1和/或ACSL1)的探针。在某些实施方案中,产品或试剂盒作为用于执行本文所述的方法的单元被推广、分配或出售。

[0117] 本文中使用的短语“基于”是指用于告知诊断决定、治疗决定的关于一种或多种生物标志物的信息、包装插页上提供的信息或营销/推广指南等。

[0118] III.方法

[0119] A.基于IRAK4通路生物标志物表达水平的诊断方法

[0120] 本发明提供了诊断方法,其中本文鉴定的IRAK4通路生物标志物用作药效学生物

标志物。

[0121] 因此,本发明的特征在于监测患有白介素-1受体相关激酶4(IRAK4)介导的疾患或病症的患者对包括IRAK4通路抑制剂治疗的反应的诊断方法,该方法包括(a)在施用第一剂量的IRAK4通路抑制剂后的时间点从患者获得的样品中,确定以下表1列出的一个或多个基因的表达水平(例如,1、2、3、4、5、6、7、8、9、10、11,12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因),和(b)比较样品中表1列出的一个或多个基因的表达水平与参考表达水平,从而监测患者对包括IRAK4通路抑制剂治疗的反应。

[0122] 表1.IRAK4通路生物标志物基因

[0123] 基因

[0124]

基因
CD38
SOCS3
AQP9
CDKN1A
GADD45B
B4GALT5
IL15RA
TNFAIP3
SOCS1
IL1RN
PFKFB3
BCL2A1
CXCL10
CCL8
GPR84
C15orf48
DRAM1
CXCL11
TNFAIP6
CSRNP1
PLSCR1
CLEC4E
SAMSN1
ACSL1

[0125] 因此,可以确定在施用第一剂量的IRAK4通路抑制剂后的时间点从患者获得的样品中选自表1列出的基因中的2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22或23个基因的任何组合的表达水平,然后比较该基因组合的表达水平与参考表达水平(例如,参考个体群中相同基因组合的中位表达水平),从而监测患者对包括IRAK4通路抑制剂治疗的反应。

[0126] 在某些情况下，方法包括在施用第一剂量的IRAK4通路抑制剂后的时间点从患者获得的样品中确定选自以下的一个或多个基因(例如，一个基因、两个基因、三个基因、四个基因、五个基因、六个基因、七个基因、八个基因、九个基因、十个基因、十一个基因或所有十二个基因)的表达水平：CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1。例如，在某些情况下，该方法包括在施用第一剂量的IRAK4通路抑制剂后的时间点从患者获得的样品中确定选自以下的一个或多个基因(例如，一个基因、两个基因、三个基因、四个基因、五个基因、六个基因、七个基因、八个基因、九个基因、十个基因或所有十一个基因)的表达水平：CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3。在特定情况下，该方法包括在施用第一剂量的IRAK4通路抑制剂后的时间点从患者获得的样品中确定选自以下的一个或多个基因(例如，一个基因、两个基因、三个基因、四个基因、五个基因、六个基因、七个基因、八个基因或所有九个基因)的表达水平：CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1。

[0127] 在一些情况下，相对于参考表达水平，在施用第一剂量的IRAK4通路抑制剂后的时间点从患者获得的样品中，表1中列出的一个或多个基因的表达水平降低。例如，在某些情况下，相对于参考表达水平(例如，在施用第一剂量的IRAK4通路抑制剂之前从患者获得的样品中表1中列出的一个或多个基因的表达水平)，表1中列出的一个或多个基因的表达水平降低了约1％或更多(例如，约2％或更多、约3％或更多、约4％或更多、约5％或更多、约6％或更多、约7％或更多、约8％或更多、约9％或更多、约10％或更多、约11％或更多、约12％或更多、约13％或更多、约14％或更多、约15％或更多、约20％或更多、约25％或更多、约30％或更多、约35％或更多、约40％或更多、约45％或更多、约50％或更多、约55％或更多、约60％或更多、约65％或更多、约70％或更多、约75％或更多、约80％或更多、约85％或更多、约90％或更多、约95％或更多、或约100％)，例如约1％至约5％、约5％至约10％、约10％至约15％、约15％至约20％、约20％至约25％、约25％至约30％、约30％至约35％、约35％至约40％、约40％至约45％、约45％至约50％、约50％至约55％、约55％至约60％、约60％至约65％、约65％至约70％、约70％至约75％、约75％至约80％、约80％至约85％、约85％至约90％、约90％至约95％、或约95％至约100％。在其他情况下，相对于参考表达水平(例如，在施用第一剂量的IRAK4通路抑制剂之前从患者获得的样品中表1中列出的一个或多个基因的表达水平)，表1中列出的一个或多个基因的表达水平降低了约0.5倍、约0.6倍、约0.7倍、约0.8倍、约0.9倍、约1倍、约1.1倍、约1.2倍、约1.3倍、约1.4倍、约1.5倍、约1.6倍、约1.7倍、约1.8倍、约1.9倍、约2倍、约2.1倍、约2.2倍、约2.3倍、约2.4倍、约2.5倍、约3倍、约3.5倍、约4倍、约4.5倍、约5倍、约5.5倍、约6倍、约6.5倍、约7倍、约7.5倍、约8倍、约8.5倍、约9倍、约9.5倍或约10倍或更大，例如约0.5倍至约0.7倍、约0.7倍至约1倍、约1倍至约1.5倍、约1.5倍至约2倍、约2倍至约3倍、约3倍至约4倍、约4倍至约5、约5倍至约6倍、约6倍至约7倍、约7倍至约8倍、或约9倍至约10倍或更大。

[0128] 在一些实施方案中，降低或减少的表达是指与参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织相比，通过如本文所述的标准技术已知的方法检测的生物标志物(例如蛋白质或核酸(例如基因或mRNA))水平总体降低约10％、20％、30％、40％、50％、60％、70％、80％、90％、95％、96％、97％、98％、99％或更高中的任意。在某些实

施方案中,降低的表达是指样品中生物标志物的表达水平(量)的降低,其中该降低是至少约0.9x、0.8x、0.7x、0.6x、0.5x、0.4x、0.3x、0.2x、0.1x、0.05x或0.01x参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织中相应生物标志物的表达水平(量)中的任意。

[0129] 在任何前述实施方案中,表1列出的一个或多个基因的降低的表达水平可表明患者对IRAK4通路抑制剂反应。因此,在一些情况下,该方法进一步包括向患者至少施用第二剂量(例如,一、二、三、四、五、六、七、八、九或十或更多其他剂量)的IRAK4通路抑制剂,所述患者的表1中列出的一个或多个基因的表达水平相对于参考表达水平降低。

[0130] 在任一前述实施方案中,参考表达水平可以是:(i)在施用第一剂量的IRAK4通路抑制剂之前从患者获得的样品中表1中列出的一个或多个基因的表达水平;(ii)在参考群中表1列出的一个或多个基因的表达水平(例如在参考群中表1列出的一个或多个基因的中位表达水平);(iii)预先指定的表1中列出的一个或多个基因的表达水平;(iv)在先前时间点从患者获得的样品中表1中列出的一个或多个基因的表达水平,其中先前时间点在施用第一剂量的IRAK4通路抑制剂之后;或(v)在随后的时间点从患者获得的样品中表1列出的一个或多个基因的表达水平。

[0131] 本发明提供了诊断方法,其中本文鉴定的IRAK4通路生物标志物用作预测生物标志物。

[0132] 因此,本发明的特征在于鉴定可从包含IRAK4通路抑制剂的治疗中受益的患有IRAK4介导的疾患或病症的患者的诊断方法,该方法包括确定从患者获得的样品中表1中列出的一个或多个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)的表达水平,其中与参考表达水平相比,样品中表1中列出的一个或多个基因的表达水平增加鉴定该患者为可从包括IRAK4通路抑制剂的治疗受益的患者。

[0133] 本发明的特征还在于为患有IRAK4介导的疾患或病症的患者选择疗法的诊断方法,该方法包括确定从患者获得的样品中表1中列出的一个或多个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)的表达水平,其中与参考表达水平相比,样品中表1中列出的一个或多个基因的表达水平增加鉴定患者为可从包括IRAK4通路抑制剂的治疗受益的患者。

[0134] 在某些情况下,鉴定患者或为患者选择疗法的方法可以包括确定选自以下的一个或多个基因(例如,一个基因、两个基因、三个基因、四个基因、五个基因、六个基因、七个基因、八个基因、九个基因、十个基因、十一个基因或所有十二个基因)的表达水平:CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、和BCL2A1。例如,在某些情况下,该方法包括确定选自以下的一个或多个基因(例如,一个基因、两个基因、三个基因、四个基因、五个基因、六个基因、七个基因、八个基因、九个基因、十个基因或所有十一个基因)的表达水平:CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3。在特定情况下,该方法包括确定选自以下的一个或多个基因(例如,一个基因、两个基因、三个基因、四个基因、五个基因、六个基因、七个基因、八个基因或所有九个基因)的表达水平:CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1。

[0135] 在某些情况下,相对于参考表达水平,从患者获得的样品中表1中列出的一个或多

个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17，18、19、20、21、22、23或所有24个基因)的表达水平增加。例如，在某些情况下，相对于参考表达水平(例如，参考群中表1列出的一个或多个基因的表达水平，例如参考群中表1列出的一个或多个基因的中位表达水平)，表1中列出的一个或多个基因的表达水平增加了约1％或更多(例如，约2％或更多、约3％或更多、约4％或更多、约5％或更多、约6％或更多、约7％或更多、约8％或更多、约9％或更多、约10％或更多、约11％或更多、约12％或更多、约13％或更多、约14％或更多、约15％或更多、约20％或更多、约25％或更多、约30％或更多、约35％或更多、约40％或更多、约45％或更多、约50％或更多、约55％或更多、约60％或更多、约65％或更多、约70％或更多、约75％或更多、约80％或更多、约85％或更多、约90％或更多、约95％或更多、或约100％)，例如约1％至约5％、约5％至约10％、约10％至约15％、约15％至约20％、约20％至约25％、约25％至约30％、约30％至约35％、约35％至约40％、约40％至约45％、约45％至约50％、约50％至约55％、约55％至约60％、约60％至约65％、约65％至约70％、约70％至约75％、约75％至约80％、约80％至约85％、约85％至约90％、约90％至约95％、或约95％至约100％。在其他情况下，相对于参考表达水平(例如，参考群中表1列出的一个或多个基因的表达水平，例如参考群中表1列出的一个或多个基因的中位表达水平)，表1中列出的一个或多个基因的表达水平增加约0.5倍、约0.6倍、约0.7倍、约0.8倍、约0.9倍、约1倍、约1.1倍、约1.2倍、约1.3倍、约1.4倍、约1.5倍、约1.6倍、约1.7倍、约1.8倍、约1.9倍、约2倍、约2.1倍、约2.2倍、约2.3倍、约2.4倍、约2.5倍、约3倍、约3.5倍、约4倍、约4.5倍、约5倍、约5.5倍、约6倍、约6.5倍、约7倍、约7.5倍、约8倍、约8.5倍、约9倍、约9.5倍或约10倍或更大，例如，约0.5倍至约0.7倍、约0.7倍至约1倍、约1倍至约1.5倍、约1.5倍至约2倍、约2倍至约3倍、约3倍至约4倍、约4倍至约5倍、约5倍至约6倍、约6倍至约7倍、约7倍至约8倍、或约9倍至约10倍或更大。在一些实施方案中，提高或增加的表达是指与参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织相比，通过如本文所述的标准本领域已知方法检测到的生物标志物(例如蛋白质或核酸(例如基因或mRNA))水平总体增加约10％、20％、30％、40％、50％、60％、70％、80％、90％、95％、96％、97％、98％、99％或更高中的任意。

[0136] 在某些实施方案中，提高或增加的表达是指样品中生物标志物的表达水平(量)的增加，其中该增加是至少约1.5x、1.75x、2x、3x、4x、5x、6x、7x、8x、9x、10x、25x、50x、75x或100x参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织中相应生物标志物的表达水平(量)中的任意。在一些实施方案中，提高的表达是指与参考样品、参考细胞、参考组织、对照样品、对照细胞、对照组织或内部对照(例如，管家基因)相比，总体增加大于约1.5倍、约1.75倍、约2倍、约2.25倍、约2.5倍、约2.75倍、约3.0倍或约3.25倍。在一些情况下，相对于参考表达水平，患者中表1中列出的一个或多个基因的表达水平增加，并且该方法进一步包括向患者施用IRAK4通路抑制剂。

[0137] 在一些实施方案中，参考表达水平可以是：(i)在参考群中表1中列出的一个或多个基因的表达水平(例如，在参考群中表1中列出的一个或多个基因的中位表达水平)；或(ii)预先指定的表1中列出的一个或多个基因的表达水平。

[0138] 以上描述的诊断方法提供了方便、有效且潜在地具有成本效益的手段，以获得可用于评估用于治疗患者的适当或有效疗法的数据和信息。例如，从患者获得的样品可以是组织样品、全血样品、血浆样品或血清样品。患者可以在用IRAK4通路抑制剂治疗之前和/或

之后取样，并且可以通过各种体外测定法检查样品，以确定患者是否可能从包括IRAK4通路抑制剂(如IRAK4抑制剂、IRAK1抑制剂、toll样受体(TLR)抑制剂、白介素-1受体(IL-1R)抑制剂、白介素-33受体(IL-33R)抑制剂或髓样分化主要反应基因88(MyD88)抑制剂)的治疗中受益。

[0139] 在另一方面，本发明还提供了用于监测患者对IRAK4通路抑制剂的敏感性的方法。该方法可以以多种测定形式进行，包括检测基因或蛋白质表达水平的测定法和检测适当活性的生化测定法。确定患者样品中表达或存在此类生物标志物可预测患者是否对IRAK4通路抑制剂的生物学效应敏感。相对于参考水平(例如，在施用第一剂量的IRAK4通路抑制剂之前从患者获得的样品中表1中列出的一个或多个基因的表达水平、在测试对IRAK4通路抑制剂敏感性的患者组/群的样品中一个或多个基因的中位表达水平、或者在患有特定的IRAK4介导的疾患或病症的患者组/群的样品中一个或多个基因的中位表达水平)，在施用第一剂量的IRAK4通路抑制剂之后的时间点从患者获得的样品中表1中列出的一个或多个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)表达中的差异或改变(即减少)与该患者用IRAK4通路抑制剂的治疗功效相关。

[0140] 在另一方面，本发明提供了一种优化对患有IRAK4介导的疾患或病症的患者的疗法的治疗功效的方法，包括检测从患者获得的以下样品中表1中列出的一个或多个基因(例如，1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)：(i)在向患者施用IRAK4通路抑制剂之前从患者获得的样品；(ii)在向患者施用IRAK4通路信号传导抑制剂之后从患者获得的样品；或(iii)在该治疗之前和之后从患者获得的样品。在向患者施用IRAK4通路抑制剂之前获得的样品中表1中列出的一个或多个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)的表达水平增加，表明该患者可能从包括IRAK4通路抑制剂的治疗中受益，并且可以相应地调整对患有IRAK4介导的疾患或病症的患者的疗法，使其包括IRAK4通路抑制剂。在其他情况下，相对于参考表达水平，在施用IRAK4通路后表1中列出的一个或多个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)的表达水平降低，表明患者对IRAK4通路抑制剂的治疗反应，可以选择继续治疗、相应调整或中止治疗。可以告知患者他们有更高的可能性对包括IRAK4通路抑制剂的治疗反应，和/或为患者提供包括IRAK4通路抑制剂治疗的建议。

[0141] 在本文所述的任何方法中，可以确定从患者获得的样品中选自表1中列出的基因中的2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22或23个基因的任何组合的表达水平。

[0142] 在本文所述的诊断方法的一些实施方案中，可以确定表1中列出的两个基因组合的表达水平，如表2中所示的任何示例性组合。

[0143] 表2 IRAK4生物标志物的示例性两基因组合

[0144]

CD38 和 SOCS3
CD38 和 AQP9
CD38 和 CDKN1A
CD38 和 GADD45B
CD38 和 B4GALT5
CD38 和 IL15RA
CD38 和 TNFAIP3
CD38 和 SOCS1
SOCS3 和 AQP9
SOCS3 和 CDKN1A
SOCS3 和 GADD45B
SOCS3 和 B4GALT5
SOCS3 和 IL15RA
SOCS3 和 TNFAIP3

[0145]

SOCS3 和 SOCS1
AQP9 和 CDKN1A
AQP9 和 GADD45B
AQP9 和 B4GALT5
AQP9 和 IL15RA
AQP9 和 TNFAIP3
AQP9 和 SOCS1
CDKN1A 和 GADD45B
CDKN1A 和 B4GALT5
CDKN1A 和 IL15RA
CDKN1A 和 TNFAIP3
CDKN1A 和 SOCS1
GADD45B 和 B4GALT5
GADD45B 和 IL15RA
GADD45B 和 TNFAIP3
GADD45B 和 SOCS1
B4GALT5 和 IL15RA
B4GALT5 和 TNFAIP3
B4GALT5 和 SOCS1
IL15RA 和 TNFAIP3
IL15RA 和 SOCS1
TNFAIP3 和 SOCS1

[0146] 在本文所述的诊断方法的一些实施方案中,可以确定表1列出的三个基因组合的

表达水平,如表3所示的任何示例性组合。

[0147] 表3 IRAK4生物标志物的示例性三基因组合

[0148]

CD38, SOCS3 和 AQP9
CD38, SOCS3 和 CDKN1A
CD38, SOCS3 和 GADD45B
CD38, SOCS3 和 B4GALT5
CD38, SOCS3 和 IL15RA
CD38, SOCS3 和 TNFAIP3
CD38, SOCS3 和 SOCS1
CD38, AQP9 和 CDKN1A
CD38, AQP9 和 GADD45B
CD38, AQP9 和 B4GALT5
CD38, AQP9 和 IL15RA
CD38, AQP9 和 TNFAIP3
CD38, AQP9 和 SOCS1

[0149]

CD38, CDKN1A 和 GADD45B
CD38, CDKN1A 和 B4GALT5
CD38, CDKN1A 和 IL15RA
CD38, CDKN1A 和 TNFAIP3
CD38, CDKN1A 和 SOCS1
CD38, GADD45B 和 B4GALT5
CD38, GADD45B 和 IL15RA
CD38, GADD45B 和 TNFAIP3
CD38, GADD45B 和 SOCS1
CD38, B4GALT5 和 IL15RA
CD38, B4GALT5 和 TNFAIP3
CD38, B4GALT5 和 SOCS1
CD38, IL15RA 和 TNFAIP3
CD38, IL15RA 和 SOCS1
CD38, TNFAIP3 和 SOCS1
SOCS3, AQP9 和 CDKN1A
SOCS3, AQP9 和 GADD45B
SOCS3, AQP9 和 B4GALT5
SOCS3, AQP9 和 IL15RA
SOCS3, AQP9 和 TNFAIP3
SOCS3, AQP9 和 SOCS1
SOCS3, CDKN1A 和 GADD45B
SOCS3, CDKN1A 和 B4GALT5
SOCS3, CDKN1A 和 IL15RA
SOCS3, CDKN1A 和 TNFAIP3
SOCS3, CDKN1A 和 SOCS1
SOCS3, GADD45B 和 B4GALT5
SOCS3, GADD45B 和 IL15RA
SOCS3, GADD45B 和 TNFAIP3
SOCS3, GADD45B 和 SOCS1
SOCS3, B4GALT5 和 IL15RA
SOCS3, B4GALT5 和 TNFAIP3
SOCS3, B4GALT5 和 SOCS1
SOCS3, IL15RA 和 TNFAIP3
SOCS3, IL15RA 和 SOCS1
SOCS3, TNFAIP3 和 SOCS1
AQP9, CDKN1A 和 GADD45B
AQP9, CDKN1A 和 B4GALT5
AQP9, CDKN1A 和 IL15RA

[0150]

AQP9, CDKN1A 和 TNFAIP3
AQP9, CDKN1A 和 SOCS1
AQP9, GADD45B 和 B4GALT5
AQP9, GADD45B 和 IL15RA
AQP9, GADD45B 和 TNFAIP3
AQP9, GADD45B 和 SOCS1
AQP9, B4GALT5 和 IL15RA
AQP9, B4GALT5 和 TNFAIP3
AQP9, B4GALT5 和 SOCS1
AQP9, IL15RA 和 TNFAIP3
AQP9, IL15RA 和 SOCS1
AQP9, TNFAIP3 和 SOCS1
CDKN1A, GADD45B 和 B4GALT5
CDKN1A, GADD45B 和 IL15RA
CDKN1A, GADD45B 和 TNFAIP3
CDKN1A, GADD45B 和 SOCS1
CDKN1A, B4GALT5 和 IL15RA
CDKN1A, B4GALT5 和 TNFAIP3
CDKN1A, B4GALT5 和 SOCS1
CDKN1A, IL15RA 和 TNFAIP3
CDKN1A, IL15RA 和 SOCS1
CDKN1A, TNFAIP3 和 SOCS1
GADD45B, B4GALT5 和 IL15RA
GADD45B, B4GALT5 和 TNFAIP3
GADD45B, B4GALT5 和 SOCS1
GADD45B, IL15RA 和 TNFAIP3
GADD45B, IL15RA 和 SOCS1
GADD45B, TNFAIP3 和 SOCS1
B4GALT5, IL15RA 和 TNFAIP3
B4GALT5, IL15RA 和 SOCS1
B4GALT5, TNFAIP3 和 SOCS1
IL15RA, TNFAIP3 和 SOCS1

[0151] 本文描述的诊断方法的一些实施方案中，可以确定表1中列出的四个基因组合的表达水平，如表4中所示的任何示例性组合。

[0152] 表4 IRAK4生物标志物的示例性四基因组合

[0153]

CD38, SOCS3, AQP9 和 CDKN1A
CD38, SOCS3, AQP9 和 GADD45B
CD38, SOCS3, AQP9 和 B4GALT5

CD38, SOCS3, AQP9 和 IL15RA
CD38, SOCS3, AQP9 和 TNFAIP3
CD38, SOCS3, AQP9 和 SOCS1
CD38, SOCS3, CDKN1A 和 GADD45B
CD38, SOCS3, CDKN1A 和 B4GALT5
CD38, SOCS3, CDKN1A 和 IL15RA
CD38, SOCS3, CDKN1A 和 TNFAIP3
CD38, SOCS3, CDKN1A 和 SOCS1
CD38, SOCS3, GADD45B 和 B4GALT5
CD38, SOCS3, GADD45B 和 IL15RA
CD38, SOCS3, GADD45B 和 TNFAIP3
CD38, SOCS3, GADD45B 和 SOCS1
CD38, SOCS3, B4GALT5 和 IL15RA
CD38, SOCS3, B4GALT5 和 TNFAIP3
CD38, SOCS3, B4GALT5 和 SOCS1
CD38, SOCS3, IL15RA 和 TNFAIP3
CD38, SOCS3, IL15RA 和 SOCS1
CD38, SOCS3, TNFAIP3 和 SOCS1
CD38, AQP9, CDKN1A 和 GADD45B
[0154] CD38, AQP9, CDKN1A 和 B4GALT5
CD38, AQP9, CDKN1A 和 IL15RA
CD38, AQP9, CDKN1A 和 TNFAIP3
CD38, AQP9, CDKN1A 和 SOCS1
CD38, AQP9, GADD45B 和 B4GALT5
CD38, AQP9, GADD45B 和 IL15RA
CD38, AQP9, GADD45B 和 TNFAIP3
CD38, AQP9, GADD45B 和 SOCS1
CD38, AQP9, B4GALT5 和 IL15RA
CD38, AQP9, B4GALT5 和 TNFAIP3
CD38, AQP9, B4GALT5 和 SOCS1
CD38, AQP9, IL15RA 和 TNFAIP3
CD38, AQP9, IL15RA 和 SOCS1
CD38, AQP9, TNFAIP3 和 SOCS1
CD38, CDKN1A, GADD45B 和 B4GALT5
CD38, CDKN1A, GADD45B 和 IL15RA
CD38, CDKN1A, GADD45B 和 TNFAIP3
CD38, CDKN1A, GADD45B 和 SOCS1
CD38, CDKN1A, B4GALT5 和 IL15RA
CD38, CDKN1A, B4GALT5 和 TNFAIP3

[0155]

CD38, CDKN1A, B4GALT5 和 SOCS1
CD38, CDKN1A, IL15RA 和 TNFAIP3
CD38, CDKN1A, IL15RA 和 SOCS1
CD38, CDKN1A, TNFAIP3 和 SOCS1
CD38, GADD45B, B4GALT5 和 IL15RA
CD38, GADD45B, B4GALT5 和 TNFAIP3
CD38, GADD45B, B4GALT5 和 SOCS1
CD38, GADD45B, IL15RA 和 TNFAIP3
CD38, GADD45B, IL15RA 和 SOCS1
CD38, GADD45B, TNFAIP3 和 SOCS1
CD38, B4GALT5, IL15RA 和 TNFAIP3
CD38, B4GALT5, IL15RA 和 SOCS1
CD38, B4GALT5, TNFAIP3 和 SOCS1
CD38, IL15RA, TNFAIP3 和 SOCS1
SOCS3, AQP9, CDKN1A 和 GADD45B
SOCS3, AQP9, CDKN1A 和 B4GALT5
SOCS3, AQP9, CDKN1A 和 IL15RA
SOCS3, AQP9, CDKN1A 和 TNFAIP3
SOCS3, AQP9, CDKN1A 和 SOCS1
SOCS3, AQP9, GADD45B 和 B4GALT5
SOCS3, AQP9, GADD45B 和 IL15RA
SOCS3, AQP9, GADD45B 和 TNFAIP3
SOCS3, AQP9, GADD45B 和 SOCS1
SOCS3, AQP9, B4GALT5 和 IL15RA
SOCS3, AQP9, B4GALT5 和 TNFAIP3
SOCS3, AQP9, B4GALT5 和 SOCS1
SOCS3, AQP9, IL15RA 和 TNFAIP3
SOCS3, AQP9, IL15RA 和 SOCS1
SOCS3, AQP9, TNFAIP3 和 SOCS1
SOCS3, CDKN1A, GADD45B 和 B4GALT5
SOCS3, CDKN1A, GADD45B 和 IL15RA
SOCS3, CDKN1A, GADD45B 和 TNFAIP3
SOCS3, CDKN1A, GADD45B 和 SOCS1
SOCS3, CDKN1A, B4GALT5 和 IL15RA
SOCS3, CDKN1A, B4GALT5 和 TNFAIP3
SOCS3, CDKN1A, B4GALT5 和 SOCS1
SOCS3, CDKN1A, IL15RA 和 TNFAIP3
SOCS3, CDKN1A, IL15RA 和 SOCS1
SOCS3, CDKN1A, TNFAIP3 和 SOCS1

SOCS3, GADD45B, B4GALT5 和 IL15RA
SOCS3, GADD45B, B4GALT5 和 TNFAIP3
SOCS3, GADD45B, B4GALT5 和 SOCS1
SOCS3, GADD45B, IL15RA 和 TNFAIP3
SOCS3, GADD45B, IL15RA 和 SOCS1
SOCS3, GADD45B, TNFAIP3 和 SOCS1
SOCS3, B4GALT5, IL15RA 和 TNFAIP3
SOCS3, B4GALT5, IL15RA 和 SOCS1
SOCS3, B4GALT5, TNFAIP3 和 SOCS1
SOCS3, IL15RA, TNFAIP3 和 SOCS1
AQP9, CDKN1A, GADD45B 和 B4GALT5
AQP9, CDKN1A, GADD45B 和 IL15RA
AQP9, CDKN1A, GADD45B 和 TNFAIP3
AQP9, CDKN1A, GADD45B 和 SOCS1
AQP9, CDKN1A, B4GALT5 和 IL15RA
AQP9, CDKN1A, B4GALT5 和 TNFAIP3
AQP9, CDKN1A, B4GALT5 和 SOCS1
AQP9, CDKN1A, IL15RA 和 TNFAIP3
AQP9, CDKN1A, IL15RA 和 SOCS1
[0156] AQP9, CDKN1A, TNFAIP3 和 SOCS1
AQP9, GADD45B, B4GALT5 和 IL15RA
AQP9, GADD45B, B4GALT5 和 TNFAIP3
AQP9, GADD45B, B4GALT5 和 SOCS1
AQP9, GADD45B, IL15RA 和 TNFAIP3
AQP9, GADD45B, IL15RA 和 SOCS1
AQP9, GADD45B, TNFAIP3 和 SOCS1
AQP9, B4GALT5, IL15RA 和 TNFAIP3
AQP9, B4GALT5, IL15RA 和 SOCS1
AQP9, B4GALT5, TNFAIP3 和 SOCS1
AQP9, IL15RA, TNFAIP3 和 SOCS1
CDKN1A, GADD45B, B4GALT5 和 IL15RA
CDKN1A, GADD45B, B4GALT5 和 TNFAIP3
CDKN1A, GADD45B, B4GALT5 和 SOCS1
CDKN1A, GADD45B, IL15RA 和 TNFAIP3
CDKN1A, GADD45B, IL15RA 和 SOCS1
CDKN1A, GADD45B, TNFAIP3 和 SOCS1
CDKN1A, B4GALT5, IL15RA 和 TNFAIP3
CDKN1A, B4GALT5, IL15RA 和 SOCS1
CDKN1A, B4GALT5, TNFAIP3 和 SOCS1

[0157]

CDKN1A, IL15RA, TNFAIP3 和 SOCS1
GADD45B, B4GALT5, IL15RA 和 TNFAIP3
GADD45B, B4GALT5, IL15RA 和 SOCS1
GADD45B, B4GALT5, TNFAIP3 和 SOCS1
GADD45B, IL15RA, TNFAIP3 和 SOCS1
B4GALT5, IL15RA, TNFAIP3 和 SOCS1

[0158] 在本文描述的诊断方法的一些实施方案中，可以确定表1中列出的五个基因组合的表达水平，如表5中所示的任何示例性组合。

[0159] 表5 IRAK4生物标志物的示例性五基因组合

[0160]

CD38, SOCS3, AQP9, CDKN1A 和 GADD45B
CD38, SOCS3, AQP9, CDKN1A 和 B4GALT5
CD38, SOCS3, AQP9, CDKN1A 和 IL15RA
CD38, SOCS3, AQP9, CDKN1A 和 TNFAIP3
CD38, SOCS3, AQP9, CDKN1A 和 SOCS1
CD38, SOCS3, AQP9, GADD45B 和 B4GALT5
CD38, SOCS3, AQP9, GADD45B 和 IL15RA
CD38, SOCS3, AQP9, GADD45B 和 TNFAIP3
CD38, SOCS3, AQP9, GADD45B 和 SOCS1
CD38, SOCS3, AQP9, B4GALT5 和 IL15RA
CD38, SOCS3, AQP9, B4GALT5 和 TNFAIP3
CD38, SOCS3, AQP9, B4GALT5 和 SOCS1
CD38, SOCS3, AQP9, IL15RA 和 TNFAIP3
CD38, SOCS3, AQP9, IL15RA 和 SOCS1
CD38, SOCS3, AQP9, TNFAIP3 和 SOCS1
CD38, SOCS3, CDKN1A, GADD45B 和 B4GALT5
CD38, SOCS3, CDKN1A, GADD45B 和 IL15RA
CD38, SOCS3, CDKN1A, GADD45B 和 TNFAIP3
CD38, SOCS3, CDKN1A, GADD45B 和 SOCS1
CD38, SOCS3, CDKN1A, B4GALT5 和 IL15RA
CD38, SOCS3, CDKN1A, B4GALT5 和 TNFAIP3
CD38, SOCS3, CDKN1A, B4GALT5 和 SOCS1
CD38, SOCS3, CDKN1A, IL15RA 和 TNFAIP3
CD38, SOCS3, CDKN1A, IL15RA 和 SOCS1
CD38, SOCS3, CDKN1A, TNFAIP3 和 SOCS1
CD38, SOCS3, GADD45B, B4GALT5 和 IL15RA
CD38, SOCS3, GADD45B, B4GALT5 和 TNFAIP3
CD38, SOCS3, GADD45B, B4GALT5 和 SOCS1
CD38, SOCS3, GADD45B, IL15RA 和 TNFAIP3

[0161]

CD38, SOCS3, GADD45B, IL15RA 和 SOCS1
CD38, SOCS3, GADD45B, TNFAIP3 和 SOCS1
CD38, SOCS3, B4GALT5, IL15RA 和 TNFAIP3
CD38, SOCS3, B4GALT5, IL15RA 和 SOCS1
CD38, SOCS3, B4GALT5, TNFAIP3 和 SOCS1
CD38, SOCS3, IL15RA, TNFAIP3 和 SOCS1
CD38, AQP9, CDKN1A, GADD45B 和 B4GALT5
CD38, AQP9, CDKN1A, GADD45B 和 IL15RA
CD38, AQP9, CDKN1A, GADD45B 和 TNFAIP3
CD38, AQP9, CDKN1A, GADD45B 和 SOCS1
CD38, AQP9, CDKN1A, B4GALT5 和 IL15RA
CD38, AQP9, CDKN1A, B4GALT5 和 TNFAIP3
CD38, AQP9, CDKN1A, B4GALT5 和 SOCS1
CD38, AQP9, CDKN1A, IL15RA 和 TNFAIP3
CD38, AQP9, CDKN1A, IL15RA 和 SOCS1
CD38, AQP9, CDKN1A, TNFAIP3 和 SOCS1
CD38, AQP9, GADD45B, B4GALT5 和 IL15RA
CD38, AQP9, GADD45B, B4GALT5 和 TNFAIP3
CD38, AQP9, GADD45B, B4GALT5 和 SOCS1
CD38, AQP9, GADD45B, IL15RA 和 TNFAIP3
CD38, AQP9, GADD45B, IL15RA 和 SOCS1
CD38, AQP9, GADD45B, TNFAIP3 和 SOCS1
CD38, AQP9, B4GALT5, IL15RA 和 TNFAIP3
CD38, AQP9, B4GALT5, IL15RA 和 SOCS1
CD38, AQP9, B4GALT5, TNFAIP3 和 SOCS1
CD38, AQP9, IL15RA, TNFAIP3 和 SOCS1
CD38, CDKN1A, GADD45B, B4GALT5 和 IL15RA
CD38, CDKN1A, GADD45B, B4GALT5 和 TNFAIP3
CD38, CDKN1A, GADD45B, B4GALT5 和 SOCS1
CD38, CDKN1A, GADD45B, IL15RA 和 TNFAIP3
CD38, CDKN1A, GADD45B, IL15RA 和 SOCS1
CD38, CDKN1A, GADD45B, TNFAIP3 和 SOCS1
CD38, CDKN1A, B4GALT5, IL15RA 和 TNFAIP3
CD38, CDKN1A, B4GALT5, IL15RA 和 SOCS1
CD38, CDKN1A, B4GALT5, TNFAIP3 和 SOCS1
CD38, CDKN1A, IL15RA, TNFAIP3 和 SOCS1
CD38, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
CD38, GADD45B, B4GALT5, IL15RA 和 SOCS1
CD38, GADD45B, B4GALT5, TNFAIP3 和 SOCS1

CD38, GADD45B, IL15RA, TNFAIP3 和 SOCS1
CD38, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
SOCS3, AQP9, CDKN1A, GADD45B 和 B4GALT5
SOCS3, AQP9, CDKN1A, GADD45B 和 IL15RA
SOCS3, AQP9, CDKN1A, GADD45B 和 TNFAIP3
SOCS3, AQP9, CDKN1A, GADD45B 和 SOCS1
SOCS3, AQP9, CDKN1A, B4GALT5 和 IL15RA
SOCS3, AQP9, CDKN1A, B4GALT5 和 TNFAIP3
SOCS3, AQP9, CDKN1A, B4GALT5 和 SOCS1
SOCS3, AQP9, CDKN1A, IL15RA 和 TNFAIP3
SOCS3, AQP9, CDKN1A, IL15RA 和 SOCS1
SOCS3, AQP9, CDKN1A, TNFAIP3 和 SOCS1
SOCS3, AQP9, GADD45B, B4GALT5 和 IL15RA
SOCS3, AQP9, GADD45B, B4GALT5 和 TNFAIP3
SOCS3, AQP9, GADD45B, B4GALT5 和 SOCS1
SOCS3, AQP9, GADD45B, IL15RA 和 TNFAIP3
SOCS3, AQP9, GADD45B, IL15RA 和 SOCS1
SOCS3, AQP9, GADD45B, TNFAIP3 和 SOCS1
SOCS3, AQP9, B4GALT5, IL15RA 和 TNFAIP3
[0162] SOCS3, AQP9, B4GALT5, IL15RA 和 SOCS1
SOCS3, AQP9, B4GALT5, TNFAIP3 和 SOCS1
SOCS3, AQP9, IL15RA, TNFAIP3 和 SOCS1
SOCS3, CDKN1A, GADD45B, B4GALT5 和 IL15RA
SOCS3, CDKN1A, GADD45B, B4GALT5 和 TNFAIP3
SOCS3, CDKN1A, GADD45B, B4GALT5 和 SOCS1
SOCS3, CDKN1A, GADD45B, IL15RA 和 TNFAIP3
SOCS3, CDKN1A, GADD45B, IL15RA 和 SOCS1
SOCS3, CDKN1A, GADD45B, TNFAIP3 和 SOCS1
SOCS3, CDKN1A, B4GALT5, IL15RA 和 TNFAIP3
SOCS3, CDKN1A, B4GALT5, IL15RA 和 SOCS1
SOCS3, CDKN1A, B4GALT5, TNFAIP3 和 SOCS1
SOCS3, CDKN1A, IL15RA, TNFAIP3 和 SOCS1
SOCS3, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
SOCS3, GADD45B, B4GALT5, IL15RA 和 SOCS1
SOCS3, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
SOCS3, GADD45B, IL15RA, TNFAIP3 和 SOCS1
SOCS3, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
AQP9, CDKN1A, GADD45B, B4GALT5 和 IL15RA
AQP9, CDKN1A, GADD45B, B4GALT5 和 TNFAIP3

[0163]

AQP9, CDKN1A, GADD45B, B4GALT5 和 SOCS1
AQP9, CDKN1A, GADD45B, IL15RA 和 TNFAIP3
AQP9, CDKN1A, GADD45B, IL15RA 和 SOCS1
AQP9, CDKN1A, GADD45B, TNFAIP3 和 SOCS1
AQP9, CDKN1A, B4GALT5, IL15RA 和 TNFAIP3
AQP9, CDKN1A, B4GALT5, IL15RA 和 SOCS1
AQP9, CDKN1A, B4GALT5, TNFAIP3 和 SOCS1
AQP9, CDKN1A, IL15RA, TNFAIP3 和 SOCS1
AQP9, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
AQP9, GADD45B, B4GALT5, IL15RA 和 SOCS1
AQP9, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
AQP9, GADD45B, IL15RA, TNFAIP3 和 SOCS1
AQP9, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
CDKN1A, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
CDKN1A, GADD45B, B4GALT5, IL15RA 和 SOCS1
CDKN1A, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
CDKN1A, GADD45B, IL15RA, TNFAIP3 和 SOCS1
CDKN1A, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1

[0164] 在本文描述的诊断方法的一些实施方案中，可以确定表1中列出的六个基因组合的表达水平，如表6中所示的任何示例性组合。

[0165] 表6 IRAK4生物标志物的示例性六基因组合

[0166]

CD38, SOCS3, AQP9, CDKN1A, GADD45B 和 B4GALT5
CD38, SOCS3, AQP9, CDKN1A, GADD45B 和 IL15RA
CD38, SOCS3, AQP9, CDKN1A, GADD45B 和 TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, GADD45B 和 SOCS1
CD38, SOCS3, AQP9, CDKN1A, B4GALT5 和 IL15RA
CD38, SOCS3, AQP9, CDKN1A, B4GALT5 和 TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, B4GALT5 和 SOCS1
CD38, SOCS3, AQP9, CDKN1A, IL15RA 和 TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, IL15RA 和 SOCS1
CD38, SOCS3, AQP9, CDKN1A, TNFAIP3 和 SOCS1
CD38, SOCS3, AQP9, GADD45B, B4GALT5 和 IL15RA
CD38, SOCS3, AQP9, GADD45B, B4GALT5 和 TNFAIP3
CD38, SOCS3, AQP9, GADD45B, B4GALT5 和 SOCS1
CD38, SOCS3, AQP9, GADD45B, IL15RA 和 TNFAIP3
CD38, SOCS3, AQP9, GADD45B, IL15RA 和 SOCS1
CD38, SOCS3, AQP9, GADD45B, TNFAIP3 和 SOCS1

CD38, SOCS3, AQP9, B4GALT5, IL15RA 和 TNFAIP3
CD38, SOCS3, AQP9, B4GALT5, IL15RA 和 SOCS1
CD38, SOCS3, AQP9, B4GALT5, TNFAIP3 和 SOCS1
CD38, SOCS3, AQP9, IL15RA, TNFAIP3 和 SOCS1
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5 和 IL15RA
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5 和 TNFAIP3
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5 和 SOCS1
CD38, SOCS3, CDKN1A, GADD45B, IL15RA 和 TNFAIP3
CD38, SOCS3, CDKN1A, GADD45B, IL15RA 和 SOCS1
CD38, SOCS3, CDKN1A, GADD45B, TNFAIP3 和 SOCS1
CD38, SOCS3, CDKN1A, B4GALT5, IL15RA 和 TNFAIP3
CD38, SOCS3, CDKN1A, B4GALT5, IL15RA 和 SOCS1
CD38, SOCS3, CDKN1A, B4GALT5, TNFAIP3 和 SOCS1
CD38, SOCS3, CDKN1A, IL15RA, TNFAIP3 和 SOCS1
CD38, SOCS3, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
CD38, SOCS3, GADD45B, B4GALT5, IL15RA 和 SOCS1
CD38, SOCS3, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
CD38, SOCS3, GADD45B, IL15RA, TNFAIP3 和 SOCS1
CD38, SOCS3, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
[0167] CD38, AQP9, CDKN1A, GADD45B, B4GALT5 和 IL15RA
CD38, AQP9, CDKN1A, GADD45B, B4GALT5 和 TNFAIP3
CD38, AQP9, CDKN1A, GADD45B, B4GALT5 和 SOCS1
CD38, AQP9, CDKN1A, GADD45B, IL15RA 和 TNFAIP3
CD38, AQP9, CDKN1A, GADD45B, IL15RA 和 SOCS1
CD38, AQP9, CDKN1A, GADD45B, TNFAIP3 和 SOCS1
CD38, AQP9, CDKN1A, B4GALT5, IL15RA 和 TNFAIP3
CD38, AQP9, CDKN1A, B4GALT5, IL15RA 和 SOCS1
CD38, AQP9, CDKN1A, B4GALT5, TNFAIP3 和 SOCS1
CD38, AQP9, CDKN1A, IL15RA, TNFAIP3 和 SOCS1
CD38, AQP9, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
CD38, AQP9, GADD45B, B4GALT5, IL15RA 和 SOCS1
CD38, AQP9, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
CD38, AQP9, GADD45B, IL15RA, TNFAIP3 和 SOCS1
CD38, AQP9, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
CD38, CDKN1A, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
CD38, CDKN1A, GADD45B, B4GALT5, IL15RA 和 SOCS1
CD38, CDKN1A, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
CD38, CDKN1A, GADD45B, IL15RA, TNFAIP3 和 SOCS1
CD38, CDKN1A, B4GALT5, IL15RA, TNFAIP3 和 SOCS1

[0168]

CD38, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5 和 IL15RA
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5 和 TNFAIP3
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5 和 SOCS1
SOCS3, AQP9, CDKN1A, GADD45B, IL15RA 和 TNFAIP3
SOCS3, AQP9, CDKN1A, GADD45B, IL15RA 和 SOCS1
SOCS3, AQP9, CDKN1A, GADD45B TNFAIP3 和 SOCS1
SOCS3, AQP9, CDKN1A, B4GALT5, IL15RA 和 TNFAIP3
SOCS3, AQP9, CDKN1A, B4GALT5, IL15RA 和 SOCS1
SOCS3, AQP9, CDKN1A, B4GALT5, TNFAIP3 和 SOCS1
SOCS3, AQP9, CDKN1A, IL15RA, TNFAIP3 和 SOCS1
SOCS3, AQP9, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
SOCS3, AQP9, GADD45B, B4GALT5, IL15RA 和 SOCS1
SOCS3, AQP9, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
SOCS3, AQP9, GADD45B, IL15RA, TNFAIP3 和 SOCS1
SOCS3, AQP9, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
SOCS3, CDKN1A, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
SOCS3, CDKN1A, GADD45B, B4GALT5, IL15RA 和 SOCS1
SOCS3, CDKN1A, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
SOCS3, CDKN1A, GADD45B, IL15RA, TNFAIP3 和 SOCS1
SOCS3, CDKN1A, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
SOCS3, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA 和 SOCS1
AQP9, CDKN1A, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
AQP9, CDKN1A, GADD45B, IL15RA, TNFAIP3 和 SOCS1
AQP9, CDKN1A, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
AQP9, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1

[0169] 在本文描述的诊断方法的一些实施方案中,可以确定表1中列出的七个基因组合的表达水平,如表7中所示的任何示例性组合。

[0170] 表7 IRAK4生物标志物的示例性七基因组合

[0171]

CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5 和 IL15RA
CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5 和 TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5 和 SOCS1
CD38, SOCS3, AQP9, CDKN1A, GADD45B, IL15RA 和 TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, GADD45B, IL15RA 和 SOCS1
CD38, SOCS3, AQP9, CDKN1A, GADD45B, TNFAIP3 和 SOCS1

[0172]

CD38, SOCS3, AQP9, CDKN1A, B4GALT5, IL15RA 和 TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, B4GALT5, IL15RA 和 SOCS1
CD38, SOCS3, AQP9, CDKN1A, B4GALT5, TNFAIP3 和 SOCS1
CD38, SOCS3, AQP9, CDKN1A, IL15RA, TNFAIP3 和 SOCS1
CD38, SOCS3, AQP9, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
CD38, SOCS3, AQP9, GADD45B, B4GALT5, IL15RA 和 SOCS1
CD38, SOCS3, AQP9, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
CD38, SOCS3, AQP9, GADD45B, IL15RA, TNFAIP3 和 SOCS1
CD38, SOCS3, AQP9, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5, IL15RA 和 SOCS1
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
CD38, SOCS3, CDKN1A, GADD45B, IL15RA, TNFAIP3 和 SOCS1
CD38, SOCS3, CDKN1A, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
CD38, SOCS3, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
CD38, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
CD38, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA 和 SOCS1
CD38, AQP9, CDKN1A, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
CD38, AQP9, CDKN1A, GADD45B, IL15RA, TNFAIP3 和 SOCS1
CD38, AQP9, CDKN1A, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
CD38, AQP9, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
CD38, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA 和 SOCS1
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
SOCS3, AQP9, CDKN1A, GADD45B, IL15RA, TNFAIP3 和 SOCS1
SOCS3, AQP9, CDKN1A, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
SOCS3, AQP9, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
SOCS3, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1

[0173] 在本文描述的诊断方法的一些实施方案中，可以确定表1中列出的八个基因组合的表达水平，如表8中所示的任何示例性组合。

[0174] 表8 IRAK4生物标志物的示例性八基因组合

[0175]

CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA 和 TNFAIP3
CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA 和 SOCS1
CD38, SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, TNFAIP3 和 SOCS1
CD38, SOCS3, AQP9, CDKN1A, GADD45B, IL15RA, TNFAIP3 和 SOCS1
CD38, SOCS3, AQP9, CDKN1A, B4GALT5, IL15RA, TNFAIP3 和 SOCS1

[0176]

CD38, SOCS3, AQP9, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
CD38, SOCS3, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
CD38, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1
SOCS3, AQP9, CDKN1A, GADD45B, B4GALT5, IL15RA, TNFAIP3 和 SOCS1

[0177] 可以通过多种方法分析样品中本文所述的IRAK4通路生物标志物的存在和/或表达水平(量),其中许多方法是本领域已知的并且是技术人员所理解的,包括但不限于,免疫组织化学("IHC")、蛋白质印迹分析、免疫沉淀、分子结合测定法、酶联免疫吸附测定法(ELISA)、酶联免疫过滤测定法(ELIFA)、荧光激活的细胞分选("FACS")、MassARRAY、蛋白质组学、基于血液的定量测定法(例如血清ELISA)、生化酶活性测定法、原位杂交、荧光原位杂交(FISH)、Southern分析、Northern分析、全基因组测序、聚合酶链反应(PCR)(包括定量PCR)(qPCR))和其他扩增类型检测方法,例如分支的DNA(branched DNA)、SISBA、TMA等)、RNA-Seq、微阵列分析、基因表达谱和/或基因表达的系列分析("SAGE")、以及可以通过蛋白质、基因和/或组织阵列分析进行的多种测定法中的任何一种。用于评估基因和基因产物状态的典型方案可见于例如Ausubel等人编辑,1995,Current Protocols In Molecular Biology,第2单元(Northern Blotting)、第4单元(Southern Blotting)、第15单元(免疫印迹)、第18单元(PCR分析)。也可以使用多重免疫测定法,如可从Rules Based Medicine或Meso Scale Discovery("MSD")获得的那些免疫测定法。

[0178] 在任何前述方法中,生物标志物(例如CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、BCL2A1、CXCL10、CCL8、GPR84、C15orf48、DRAM1、CXCL11、TNFAIP6、CSRNP1、PLSCR1、CLEC4E、SAMSN1和/或ACSL1)的存在和/或表达水平(量)可以是核酸表达水平。在一些情况下,使用qPCR、RT-PCR、RNA-Seq、多重qPCR或RT-qPCR、微阵列分析、SAGE、MassARRAY技术或原位杂交(例如,FISH)来确定核酸表达水平。

[0179] 在特定情况下,生物标志物(例如CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、BCL2A1、CXCL10、CCL8、GPR84、C15orf48、DRAM1、CXCL11、TNFAIP6、CSRNP1、PLSCR1、CLEC4E、SAMSN1和/或ACSL1)的表达水平是mRNA表达水平。评估细胞中mRNA的方法是众所周知的,包括例如qPCR、使用二代测序技术的RNA-Seq(例如整个转录组弹枪测序)、使用互补DNA探针的杂交测定法(如使用对一个或多个基因特异的标记的核糖探针的原位杂交、Northern印迹法和相关技术)和各种核酸扩增测定法(如使用对一个或多个基因特异的互补引物的RT-PCR,以及其他扩增型检测方法,例如分支的DNA、SISBA、TMA等)。另外,这样的方法可以包括一个或多个允许测定生物样品中靶mRNA的水平的步骤,例如,通过同时检查"管家"基因(例如肌动蛋白家族成员)的相当的对照mRNA序列的水平。任选地,可以确定扩增的靶cDNA的序列。可选方法包括通过微阵列技术检查或检测组织或细胞样品中的mRNA(如靶mRNA)的方案。使用核酸微阵列测试,将来自测试和对照组织样品的测试和对照mRNA样品逆转录并标记以产生cDNA探针。然后将探针与固定在固体支持物上的核酸阵列杂交。配置阵列,以便使阵列中每个成员的顺序和位置是已知的。例如,可以在固体支持物上排列选择的基因,其表达与增加或降低的包括IRAK4通路抑制剂的治疗的临床益处相关。标记探针与特定阵列成员的杂交表明衍生探针的样品表达该基因。

[0180] 在任何前述方法中，通过测定生物标志物的蛋白质表达水平来测量生物标志物(例如CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、BCL2A1、CXCL10、CCL8、GPR84、C15orf48、DRAM1、CXCL11、TNFAIP6、CSRNP1、PLSCR1、CLEC4E、SAMSN1和/或ACSL1)的存在和/或表达水平(量)。在某些情况下，该方法包括在允许结合生物标志物的条件下，使生物样品与特异性结合本文所述的生物标志物的抗体接触，并检测抗体和生物标志物之间是否形成复合物。这样的方法可以是体外或体内方法。可以使用本领域已知的任何测量蛋白质表达水平的方法。例如，在某些情况下，使用选自以下的方法测定生物标志物(例如，CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3、BCL2A1、CXCL10、CCL8、GPR84、C15orf48、DRAM1、CXCL11、TNFAIP6、CSRNP1、PLSCR1、CLEC4E、SAMSN1和/或ACSL1)的蛋白质表达水平：流式细胞术(例如，荧光激活细胞分选(FACS™))、蛋白印迹、ELISA、ELIFA、免疫沉淀、免疫组织化学(IHC)、免疫荧光、放射免疫测定法、斑点印迹、免疫检测方法、HPLC、表面等离子体共振、光谱、质谱和HPLC。

[0181] 在某些情况下，参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织是来自相同受试者或个体的单个样品或多个样品的组合，其在一个或多个与获得测试样品不同的时间点上获得。例如，在比获得测试样品更早的时间点从相同受试者或个体获得参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织。如果参考样品在初始诊断IRAK4介导的疾患或病症的过程中获得、而测试样品在后来IRAK4介导的疾患或病症变得更严重时获得，则这些参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织可能是有用的。

[0182] 在某些实施方案中，参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织是来自不是患者的一个或多个健康个体的多个样品的组合。在某些实施方案中，参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织是来自不是患者或病患的一个或多个患有疾患或病症(例如IRAK4介导的疾患或病症)的个体的多个样品的组合。在某些实施方案中，参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织是来自正常组织的合并RNA样品或来自不是患者的一个或多个个体的合并血浆或血清样品。在某些实施方案中，参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织是来自不是患者的患有IRAK4介导的疾患或病症(例如，炎性疾患或免疫疾患)的一个或多个个体的合并血浆或血清样品的合并RNA样品。在某些实施方案中，参考水平是一组样品中生物标志物表达的中位水平。在某些实施方案中，参考水平是患有特定疾病或病症(例如IRAK4介导的疾患或病症(例如炎性疾患或免疫疾患))的患者群中生物标志物表达的中位水平。

[0183] 在任何前述诊断方法中，IRAK4介导的疾患或病症选自免疫疾患、炎性疾患、纤维化疾患、嗜酸性细胞疾患、感染、疼痛、中枢神经系统疾患、急性肾脏损伤、慢性肾脏疾患、子宫内膜异位、非酒精性脂肪肝疾病、代谢综合征和肥胖。

[0184] 在某些情况下，免疫疾患是过敏性气道综合征、过敏性鼻炎、同种异体移植排斥、哮喘、特应性皮炎、接触性皮炎、克罗恩氏病、皮肤狼疮、迟发性超敏反应、糖尿病、痛风、移植物抗宿主病、移植物排斥、炎性肠疾病(IBD)、炎性肌炎(例如，多肌炎、皮肌炎)、狼疮、狼疮肾炎、多发性硬化症、牛皮癣、类风湿性关节炎、硬皮病、败血症、系统性红斑狼疮、全身性

硬化或溃疡性结肠炎。

[0185] 在某些情况下，炎性疾患是急性呼吸窘迫综合征、急性肺损伤、成人斯蒂尔病、过敏性气道综合征、过敏性鼻炎、哮喘、动脉粥样硬化、特应性皮炎、支气管炎、焦磷酸钙沉积病(CPPD)、脑血管意外(例如，中风)、慢性阻塞性肺病(COPD)、接触性皮炎、克罗恩氏病、冷冻蛋白相关的周期性综合征(CAPS)、皮肤狼疮、迟发性超敏反应、痛风、移植物抗宿主病、炎性肠疾病(IBD)、炎性肌炎(例如，多发性肌炎、皮肌炎)、狼疮、狼疮肾炎、类风湿性关节炎、鼻炎、硬皮病、败血症、系统性红斑狼疮、全身发作的幼年特发性关节炎、全身性硬化或溃疡性结肠炎。

[0186] 在某些情况下，嗜酸性细胞疾患是过敏性鼻炎、哮喘、特应性皮炎、慢性阻塞性肺病(COPD)或接触性皮炎。

[0187] 在某些情况下，纤维化疾患是动脉粥样硬化、硬皮病或全身性硬化。

[0188] 在某些情况下，中枢神经系统疾患是脑血管意外(例如中风)、多发性硬化症或神经变性。

[0189] 在某些情况下，疼痛是神经性疼痛。

[0190] 在某些情况下，感染是支气管炎或败血症。

[0191] 在本发明的任何前述诊断方法中，IRAK4通路抑制剂是IRAK4抑制剂、IRAK1抑制剂、toll样受体(TLR)抑制剂、白介素-1受体(IL-1R)抑制剂、白介素-33受体(IL-33R)抑制剂、或髓样分化主要反应基因88(MyD88)抑制剂。在一个实例中，IRAK4通路抑制剂是IRAK4抑制剂。在一些情况下，IRAK4通路抑制剂是TLR抑制剂。在一些情况下，TLR抑制剂是TLR7抑制剂、TLR8抑制剂、TLR9抑制剂、TLR1抑制剂、TLR2抑制剂、TLR4抑制剂、TLR5抑制剂、TLR6抑制剂或TLR10抑制剂。在某些情况下，IRAK4通路抑制剂是TLR7抑制剂、TLR8抑制剂或TLR7和TLR8两者的抑制剂。在某些情况下，IRAK4通路抑制剂是TLR9抑制剂。在任何前述实施方案中，IRAK4通路抑制剂是小分子抑制剂。在其他实施方案中，IRAK4通路抑制剂是蛋白或多蛋白复合物，如抗体。

[0192] B.使用IRAK4通路抑制剂的治疗方法

[0193] 本发明还提供了用于治疗患有IRAK4介导的疾患或病症(例如免疫疾患(例如系统性红斑狼疮(SLE))或炎性疾患(例如哮喘))的患者的方法。因此，在某些情况下，本发明的方法包括向患者施用IRAK4通路抑制剂。以上描述的或本领域已知的任何IRAK4通路抑制剂可以与该方法结合使用。

[0194] 在一个方面，本发明的特征在于一种使用IRAK4通路抑制剂治疗患有IRAK4介导的疾患或病症的患者的方法，该方法(a)测定在施用第一剂量的IRAK4通路抑制剂后的时间点上从患者获得的样品中，表1中列出的一个或多个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)的表达水平；(b)比较样品中表1中列出的一个或多个基因的表达水平与参考表达水平；和(c)基于相对于参考表达水平表1中列出的一个或多个基因的表达水平降低，向患者至少施用第二剂量的IRAK4通路抑制剂。

[0195] 在一些情况下，相对于参考表达水平，在施用第一剂量的IRAK4通路抑制剂后的时间点从患者获得的样品中，表1中列出的一个或多个基因的表达水平降低。例如，在某些情况下，相对于参考表达水平(例如，在施用第一剂量的IRAK4通路抑制剂之前从患者获得的样品中表1中列出的一个或多个基因的表达水平)，表1中列出的一个或多个基因的表达水

平降低了约1%或更多(例如约2%或更多、约3%或更多、约4%或更多、约5%或更多、约6%或更多、约7%或更多、约8%或更多、约9%或更多、约10%或更多、约11%或更多、约12%或更多、约13%或更多、约14%或更多、约15%或更多、约20%或更多、约25%或更多、约30%或更多、约35%或更多、约40%或更多、约45%或更多、约50%或更多、约55%或更多、约60%或更多、约65%或更多、约70%或更多、约75%或更多、约80%或更多、约85%或更多、约90%或更多、约95%或更多、或约100%)，例如约1%至约5%、约5%至约10%、约10%至约15%、约15%至约20%、约20%至约25%、约25%至约30%、约30%至约35%、约35%至约40%、约40%至约45%、约45%至约50%、约50%至约55%、约55%至约60%、约60%至约65%、约65%至约70%、约70%至约75%、约75%至约80%、约80%至约85%、约85%至约90%、约90%至约95%、或约95%至约100%。在其他情况下，相对于参考表达水平(例如，在施用第一剂量的IRAK4通路抑制剂之前从患者获得的样品中表1列出的一种或多种基因的表达水平)，表1中列出的一个或多个基因的表达水平降低约0.5倍、约0.6倍、约0.7倍、约0.8倍、约0.9倍、约1倍、约1.1倍、约1.2倍、约1.3倍、约1.4倍、约1.5倍、约1.6倍、约1.7倍、约1.8倍、约1.9倍、约2倍、约2.1倍、约2.2倍、约2.3倍、约2.4倍、约2.5倍、约3倍、约3.5倍、约4倍、约4.5倍、约5倍、约5.5倍、约6倍、约6.5倍、约7倍、约7.5倍、约8倍、约8.5倍、约9倍、约9.5倍或约10倍或更大，例如约0.5倍至约0.7倍、约0.7倍至约1倍、约1倍至约1.5倍、约1.5倍至约2倍、约2倍至约3倍、约3倍至约4倍、约4倍至约5倍、约5倍至约6倍、约6倍至约7倍、约7倍至约8倍、或约9倍至约10倍或更大。

[0196] 在一些实施方案中，降低或减少的表达是指与参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织相比，通过如本文所述的标准技术已知方法检测到的生物标志物(例如蛋白质或核酸(例如基因或mRNA))的水平总体降低约10%、20%、30%、40%、50%、60%、70%、80%、90%、95%、96%、97%、98%、99%或更高中的任意。在某些实施方案中，降低的表达是指样品中生物标志物的表达水平(量)的降低，其中该降低至少约为0.9x、0.8x、0.7x、0.6x、0.5x、0.4x、0.3x、0.2x、0.1x、0.05x或0.01x参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织中相应生物标志物的表达水平(量)中的任意。

[0197] 在某些情况下，方法包括基于相对于参考表达水平降低的表1中列出的一个或多个基因的表达水平，向已接受第一剂量的IRAK4通路抑制剂的患有IRAK4介导的疾患或病症的患者至少施用第二剂量的IRAK4通路抑制剂。在一些情况下，该方法包括基于相对于参考表达水平降低的选自以下的一个或多个基因(例如，一个基因、两个基因、三个基因、四个基因、五个基因、六个基因、七个基因、八个基因、九个基因、十个基因、十一个基因或所有十二个基因)的表达水平:CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1，向已接受第一剂量的IRAK4通路抑制剂的患有IRAK4介导的疾患或病症的患者至少施用第二剂量的IRAK4通路抑制剂。在某些情况下，该方法包括基于相对于参考表达水平降低的选自以下的一个或多个基因(例如，一个基因、两个基因、三个基因、四个基因、五个基因、六个基因、七个基因、八个基因、九个基因、十个基因或所有十一个基因)的表达水平:CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3，向已接受第一剂量的IRAK4通路抑制剂的患有IRAK4介导的疾患或病症的患者至少施用第二剂量的IRAK4通路抑制剂。在其他情况下，该方法包括基于相对于

参考表达水平降低的选自以下的一个或多个基因(例如,一个基因、两个基因、三个基因、四个基因、五个基因、六个基因、七个基因、八个基因或所有九个基因)的表达水平:CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1,向已接受第一剂量的IRAK4通路抑制剂的患有IRAK4介导的疾患或病症的患者至少施用第二剂量的IRAK4通路抑制剂。

[0198] 在任何前述实施方案中,参考表达水平可以是:(i)在施用第一剂量的IRAK4通路抑制剂之前从患者获得的样品中表1中列出的一个或多个基因的表达水平;(ii)在参考群中表1列出的一个或多个基因的表达水平(例如在参考群中表1列出的一个或多个基因的中位表达水平);(iii)预先指定的表1中列出的一个或多个基因的表达水平;(iv)在先前时间点从患者获得的样品中表1中列出的一个或多个基因的表达水平,其中先前时间点在施用第一剂量的IRAK4通路抑制剂之后;或(v)在随后的时间点从患者获得的样品中表1列出的一个或多个基因的表达水平。

[0199] 在另一方面,本发明的特征在于治疗患有IRAK4介导的疾患或病症的患者的治疗方法,该方法包括向患者施用IRAK4通路抑制剂,其中在治疗之前已经确定,相对于参考表达水平从患者获得的样品中表1列出的一个或多个基因(例如,1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)的表达水平增加。

[0200] 在某些情况下,已经确定相对于参考表达水平,从患者获得的样品中表1列出的一个或多个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)的表达水平增加。例如,在某些情况下,已确定相对于参考表达水平(例如,参考群中表1中列出的一个或多个基因的表达水平,例如,参考群中表1中列出的一个或多个基因的中位表达水平),表1中列出的一个或多个基因的表达水平增加了约1%或更多(例如,约2%或更多、约3%或更多、约4%或更多、约5%或更多、约6%或更多、约7%或更多、约8%或更多、约9%或更多、约10%或更多、约11%或更多、约12%或更多、约13%或更多、约14%或更多、约15%或更多、约20%或更多、约25%或更多、约30%或更多、约35%或更多、约40%或更多、约45%或更多、约50%或更多、约55%或更多、约60%或更多、约65%或更多、约70%或更多、约75%或更多、约80%或更多、约85%或更多、约90%或更多、约95%或更多、或约100%),例如约1%至约5%、约5%至约10%、约10%至约15%、约15%至约20%、约20%至约25%、约25%至约30%、约30%至约35%、约35%至约40%、约40%至约45%、约45%至约50%、约50%至约55%、约55%至约60%、约60%至约65%、约65%至约70%、约70%至约75%、约75%至约80%、约80%至约85%、约85%至约90%、约90%至约95%、或约95%至约100%。在其他情况下,已经确定相对于参考表达水平(例如,参考群中表1中列出的一个或多个基因的表达水平,例如,参考群中表1中列出的一个或多个基因的中位表达水平),表1中列出的一个或多个基因的表达水平增加约0.5倍、约0.6倍、约0.7倍、约0.8倍、约0.9倍、约1倍、约1.1倍、约1.2倍、约1.3倍、约1.4倍、约1.5倍、约1.6倍、约1.7倍、约1.8倍、约1.9倍、约2倍、约2.1倍、约2.2倍、约2.3倍、约2.4倍、约2.5倍、约3倍、约3.5倍、约4倍、约4.5倍、约5倍、约5.5倍、约6倍、约6.5倍、约7倍、约7.5倍、约8倍、约8.5倍、约9倍、约9.5倍或约10倍或更大,例如,约0.5倍至约0.7倍、约0.7倍至约1倍、约1倍至约1.5倍、约1.5倍至约2倍、约2倍至约3倍、约3倍至约4倍、约4倍至约5倍、约5倍至约6倍、约6倍至约7倍、约7倍至约8倍、或约9倍至约10倍或更大。在一些实施方案中,提高或增加的表达是指与

参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织相比，通过如本文所述的标准技术已知的方法检测到的生物标志物(例如蛋白质或核酸(例如基因或mRNA))水平总体增加约10％、20％、30％、40％、50％、60％、70％、80％、90％、95％、96％、97％、98％、99％或更高中的任意。

[0201] 在某些实施方案中，提高或增加的表达是指样品中生物标志物的表达水平(量)的增加，其中该增加是至少约1.5x、1.75x、2x、3x、4x、5x、6x、7x、8x、9x、10x、25x、50x、75x或100x参考水平、参考样品、参考细胞、参考组织、对照样品、对照细胞或对照组织中相应的生物标志物的表达水平(量)。在一些实施方案中，提高的表达是指与参考样品、参考细胞、参考组织、对照样品、对照细胞、对照组织或内部对照(例如，管家基因)相比，总体增加大于约1.5倍、约1.75倍、约2倍、约2.25倍、约2.5倍、约2.75倍、约3.0倍或约3.25倍。

[0202] 在某些实施方案中，当相对于参考表达水平表1中列出的一个或多个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)的表达水平增加，将患者鉴定为具有增加的受益于IRAK4通路抑制剂治疗的可能性时，该方法包括向所述患者施用IRAK4通路抑制剂。

[0203] 在某些情况下，当相对于参考表达水平选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN、PFKFB3和BCL2A1中的一个或多个基因(例如一个基因、两个基因、三个基因、四个基因、五个基因、六个基因、七个基因、八个基因、九个基因、十个基因、十一个基因或所有十二个基因)的表达水平增加，将患者鉴定为具有增加的受益于IRAK4通路抑制剂治疗的可能性时，该方法包括向患有IRAK4介导的疾患或病症的患者施用IRAK4通路抑制剂。在一些情况下，当相对于参考表达水平选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3、SOCS1、IL1RN和PFKFB3中的一个或多个基因(例如一个基因、两个基因、三个基因、四个基因、五个基因、六个基因、七个基因、八个基因、九个基因、十个基因或所有十一个基因)的表达水平增加，将患者鉴定为具有增加的受益于IRAK4通路抑制剂治疗的可能性时，该方法包括向患有IRAK4介导的疾患或病症的患者施用IRAK4通路抑制剂。在一些情况下，当相对于参考表达水平选自CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1中的一个或多个基因(例如一个基因、两个基因、三个基因、四个基因、五个基因、六个基因、七个基因、八个基因或所有九个基因)的表达水平增加，将患者鉴定为具有增加的受益于IRAK4通路抑制剂治疗的可能性时，该方法包括向患有IRAK4介导的疾患或病症的患者施用IRAK4通路抑制剂。

[0204] 在一些实施方案中，参考表达水平可以是：(i)在参考群中表1中列出的一个或多个基因的表达水平(例如，在参考群中表1中列出的一个或多个基因的中位表达水平)；或(ii)预先指定的表1中列出的一个或多个基因的表达水平。

[0205] 在上述任何方法中，IRAK4通路抑制剂的施用可具有以下治疗效果(即益处)：由于IRAK4通路抑制剂的治疗、或作为其治疗结果，患者具有细胞或生物学反应、完全反应、部分反应、稳定的疾病(无进展或复发)或后期复发的反应。对于IRAK4介导的特定疾患或病症，根据标准医学实践，通过不同方式评估和评价对IRAK4通路抑制剂治疗的反应性。通常，技术医生将寻求特定疾病体征和症状的减轻。以下是示例。

[0206] 对于IRAK4介导的狼疮和SLE疾患，SLEDAI评分提供数值量化的疾病活动。SLEDAI是已知与疾病活动相关的24个临床和实验室参数的加权指数，数值范围为0-103。参见

Bryan Gescuk&John Davis,“Novel therapeutic agent for systemic lupus erythematosus”in Current Opinion in Rheumatology 2002,14:515-521。据信双链DNA的抗体会引起肾脏损伤(flare)和狼疮的其他表现。可以监测接受抗体治疗的患者的肾脏损伤时间,其指血清肌酐、尿蛋白或尿液中血液的显著可再现增加。替代地或另外,可以监测患者的抗核抗体水平和双链DNA的抗体的水平。

[0207] 对于IRAK4介导的类风湿关节炎(RA)疾患,治疗进展的测量可能包括肿胀和疼痛的关节数量以及晨僵的长度。通过使用X射线和称为Sharp评分的评分系统,可以检查患者手脚关节的侵蚀程度。另一个评分系统是基于美国风湿病学会评估治疗反应的标准。一种评估RA治疗功效的方法是基于美国风湿病学会(ACR)的标准,除其他之外,该标准测量疼痛和肿胀关节的改善百分比。与未进行抗体治疗(例如治疗前的基线)或使用安慰剂治疗相比,RA患者的评分为例如ACR20(20%改善)。评估抗体治疗功效的其他方法包括X射线评分,如用于对结构损伤(如骨侵蚀和关节间隙变窄)进行评分的Sharp X射线评分。还可以根据在治疗期间或之后的健康评估问卷[HAQ]评分、AIMS评分、SF-36评估对患者的残疾的预防或改善。ACR20标准可包括:疼痛(疼)关节计数和肿胀关节计数改善20%,以及以下5种其他测量中的至少3种改善20%:

[0208] 1.通过视觉模拟量表(VAS)评估患者的疼痛,

[0209] 2.患者对疾患活动的整体评估(VAS),

[0210] 3.医师对疾患活动的整体评估(VAS),

[0211] 4.通过健康评估问卷测量患者自我评估的残疾,和

[0212] 5.急性期反应物、CRP或ESR。

[0213] 类似地定义ACR 50和70。优选地,向患者施用一定量的本发明的CD20结合抗体,以有效地获得至少ACR20的评分,优选至少ACR30,更优选至少ACR50,甚至更优选至少ACR70,最优选至少ACR 75及更高。

[0214] 在一些情况下,与不包含IRAK4通路抑制剂的治疗相比,施用IRAK4通路抑制剂具有将IRAK4介导的疾患或病症的进展降低或延迟1天或更长时间(例如2天、3天、4天、5天、6天、1周、2周、3周、1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月或1年或以上)的治疗作用。

[0215] 在任何前述治疗方法中,IRAK4介导的疾患或病症选自免疫疾患、炎性疾患、纤维化疾患、嗜酸性细胞疾患、感染、疼痛、中枢神经系统疾患、急性肾脏损伤、慢性肾脏疾病、子宫内膜异位症、非酒精性脂肪肝疾病、代谢综合征和肥胖。

[0216] 在某些情况下,免疫疾患是过敏性气道综合征、过敏性鼻炎、同种异体移植排斥、哮喘、特应性皮炎、接触性皮炎、克罗恩氏病、皮肤狼疮、迟发性超敏反应、糖尿病、痛风、移植物抗宿主病、移植物排斥、炎性肠疾病(IBD)、炎性肌炎(例如,多肌炎、皮肌炎)、狼疮、狼疮肾炎、多发性硬化症、牛皮癣、类风湿性关节炎、硬皮病、败血症、系统性红斑狼疮、全身性硬化或溃疡性结肠炎。

[0217] 在某些情况下,炎性疾患是急性呼吸窘迫综合征、急性肺损伤、成人斯蒂尔病、过敏性气道综合征、过敏性鼻炎、哮喘、动脉粥样硬化、特应性皮炎、支气管炎、焦磷酸钙沉积病(CPPD)、脑血管意外(例如,中风)、慢性阻塞性肺病(COPD)、接触性皮炎、克罗恩氏病、冷冻蛋白相关的周期性综合征(CAPS)、皮肤狼疮、迟发性超敏反应、痛风、移植物抗宿主病、炎

性肠疾病(IBD)、炎性肌炎(例如,多发性肌炎、皮肌炎)、狼疮、狼疮肾炎、类风湿性关节炎、鼻炎、硬皮病、败血症、系统性红斑狼疮、全身发作的幼年特发性关节炎、全身性硬化或溃疡性结肠炎。

[0218] 在某些情况下,嗜酸性细胞疾患是过敏性鼻炎、哮喘、特应性皮炎、慢性阻塞性肺病(COPD)或接触性皮炎。

[0219] 在某些情况下,纤维化疾患是动脉粥样硬化、硬皮病或全身性硬化。

[0220] 在某些情况下,中枢神经系统疾患是脑血管意外(例如中风)、多发性硬化症或神经变性。

[0221] 在某些情况下,疼痛是神经性疼痛。

[0222] 在某些情况下,感染是支气管炎或败血症。

[0223] 如上所述,IRAK4通路抑制剂可以是IRAK4抑制剂、IRAK1抑制剂、toll样受体(TLR)抑制剂、白介素-1受体(IL-1R)抑制剂、白介素-33受体(IL-33R)抑制剂、或髓样分化主要反应基因88(MyD88)抑制剂。在一个情况中,IRAK4通路抑制剂是IRAK4抑制剂。在一些情况下,IRAK4通路抑制剂是TLR抑制剂。在一些情况下,TLR抑制剂是TLR7抑制剂、TLR8抑制剂、TLR9抑制剂、TLR1抑制剂、TLR2抑制剂、TLR4抑制剂、TLR5抑制剂、TLR6抑制剂或TLR10抑制剂。在某些情况下,IRAK4通路抑制剂是TLR7抑制剂、TLR8抑制剂或TLR7抑制剂和TLR8抑制剂两者。在某些情况下,IRAK4通路抑制剂是TLR9抑制剂。在任何前述实施方案中,IRAK4通路抑制剂是小分子抑制剂。在其他实施方案中,IRAK4通路抑制剂是蛋白或多蛋白复合物,如抗体。

[0224] 剂量和施用

[0225] 一旦鉴定了对IRAK4通路抑制剂治疗反应或敏感的患者,就可以单独或与其他治疗剂组合使用IRAK4通路抑制剂进行治疗。这种治疗可导致,例如,与不包括IRAK4通路抑制剂的治疗相比,降低或延迟IRAK4介导的疾患或病症的进展1天或更长时间(例如2天、3天、4天、5天、6天、1周、2周、3周、1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月或1年或更长时间)。此外,用IRAK4通路抑制剂和至少一种其他治疗剂的组合进行治疗优选使患者产生附加的、更优选协同的(或大于附加的)治疗益处。优选地,在该组合方法中,至少一次施用IRAK4通路抑制剂和至少一种其他治疗剂之间的时间为约一个月或更短,更优选地为约两周或更短。

[0226] 本领域技术人员将理解,在诊断患者可能对IRAK4通路抑制剂反应后,将由主治医师决定向其施用治疗有效量的IRAK4通路抑制剂的确切方式。患者对这种IRAK4通路抑制剂的可能反应的诊断以及患者的病症和病史可能影响施用模式,包括剂量、与其他药剂的组合、施用的时机和频率等。因此,即使患有IRAK4介导的疾患或病症(例如,免疫疾患(例如,SLE)或炎性疾患(例如,哮喘))的患者被预测对IRAK4通路抑制剂相对不敏感,但其仍然可能从该IRAK4通路抑制剂治疗中受益,特别是与其他药剂(包括可能改变患者对拮抗剂反应性的药剂)组合使用。

[0227] 以符合良好医疗规范的方式配制、给药和施用包含IRAK4通路抑制剂的组合物。在此情况下考虑的因素包括所治疗IRAK4介导的疾患或病症的特定类型(例如,免疫疾患、炎性疾患、纤维化疾患、嗜酸性细胞疾患、感染、疼痛、中枢神经系统疾患、急性肾脏损伤、慢性肾脏疾病、子宫内膜异位、非酒精性脂肪肝疾病、代谢综合征和肥胖症)、所治疗的特定哺乳

动物(例如人)、个体患者的临床状况、IRAK4介导的疾患或病症的原因、物质递送的部位、可能的副作用、抑制剂的类型、施用方法、施用时间表以及医疗从业人员已知的其他因素。施用的IRAK4通路抑制剂的有效量将由这些考虑因素决定。

[0228] 具有本领域一般技能的医师可以基于如所使用的IRAK4通路抑制剂的特定类型等因素,容易地确定所需的药物组合物的有效量并开处方。例如,医师可以以低于为获得期望治疗效果所需水平的药物组合物中使用的IRAK4通路抑制剂的剂量开始,并逐渐增加剂量直至获得期望的效果。可以例如通过使用功效的标准测量评估患者的体征和症状来确定抑制剂的给药剂量或治疗方案的有效性。

[0229] 在某些实例中,IRAK4通路抑制剂可以是施用于受试者的唯一药剂(即,作为单一疗法)。

[0230] 在某些实例中,用相同的IRAK4通路抑制剂治疗患者至少两次。因此,第一和第二剂量的IRAK4通路抑制剂优选使用相同的IRAK4通路抑制剂(或至少相同种类/类型的IRAK4通路抑制剂,例如,使用相同或不同的IRAK4抑制剂的剂量),更优选所有剂量的IRAK4通路抑制剂使用相同的IRAK4通路抑制剂,即前两个剂量(优选所有剂量)的治疗均使用一种类/类型的IRAK4通路抑制剂(例如,所有剂量使用相同或不同的IRAK4抑制剂)。

[0231] 可以根据标准方法使用IRAK4通路抑制剂或其可药用盐进行治疗。

[0232] 如果提供多个剂量的IRAK4通路抑制剂,则可以使用相同或不同的施用方式来提供每个剂量。在一个实施方案中,通过口服施用每个剂量。在一个实施方案中,通过静脉内施用每个剂量。在另一个实施方案中,通过皮下施用给予每个剂量。在又一个实施方案中,通过静脉内和皮下施用给予所述剂量。

[0233] 只要医学上指定,就可以继续治疗的持续时间,或者继续治疗的持续时间到获得期望的治疗效果(例如,本文所述的那些)。在某些实施方案中,治疗持续1个月、2个月、4个月、6个月、8个月、10个月、1年、2年、3年、4年、5年、或长达数年时间,直至受试者一生。

[0234] 但是,如上所述,这些建议的IRAK4通路抑制剂的量经过大量的疗法研判。如上所述,选择合适剂量和时间表的关键因素是获得的结果。在一些实施方案中,在尽可能接近被治疗的IRAK4介导的疾患或病症(例如,免疫疾患、炎性疾患、纤维化疾患、嗜酸性细胞疾患、感染、疼痛、中枢神经系统疾患、急性肾脏损伤、慢性肾脏疾病、子宫内膜异位症、非酒精性脂肪肝疾病、代谢综合征和肥胖症)的首次体征、诊断、表现或发生时施用IRAK4通路抑制剂。

[0235] 1.施用路径

[0236] 可以以与良好医疗实践一致的方式配制、给药和施用IRAK4通路抑制剂和任何其他治疗剂。在此情况下考虑的因素包括治疗的特定IRAK4介导的疾患或病症(例如,免疫疾患、炎性疾患、纤维化疾患、嗜酸性细胞疾患、感染、疼痛、中枢神经系统疾患、急性肾脏损伤、慢性肾脏疾病、子宫内膜异位症、非酒精性脂肪肝疾病、代谢综合征和肥胖症)、个体患者的临床状况、疾患原因、物质递送的部位、施用方法、施用时间表以及医疗从业人员已知的其他因素。IRAK4通路抑制剂可选地、但不是必须地、与一种或多种目前用于预防或治疗所治疗的IRAK4介导的疾患或病症(例如免疫疾患、炎性疾患、纤维化疾患、嗜酸性细胞疾患、感染、疼痛、中枢神经系统疾患、急性肾脏损伤、慢性肾脏疾病、子宫内膜异位症、非酒精性脂肪肝疾病、代谢综合征和肥胖症)的药剂一起配制,和/或同时施用。

[0237] 为了预防或治疗所治疗的IRAK4介导的疾患或病症(例如免疫疾患、炎性疾患、纤维化疾患、嗜酸性细胞疾患、感染、疼痛、中枢神经系统疾患、急性肾脏损伤、慢性肾脏疾病、子宫内膜异位症、非酒精性脂肪肝疾病、代谢综合征和肥胖症),本文所述的IRAK4通路抑制剂的适当剂量(当单独使用或与一种或多种其他治疗剂组合使用时)将取决于待治疗疾病的类型、疾病的严重程度和病程、IRAK4通路抑制剂是用于预防还是治疗目的施用、既往治疗、患者的临床病史和对IRAK4通路抑制剂的反应、以及主治医师的判断。IRAK4通路抑制剂适合一次或通过一系列治疗施用于患者。对于经过几天或更长时间的重复施用,根据状况,治疗通常持续至出现期望的疾病症状抑制。这样的剂量可以例如每周或每三周间歇地施用(例如,使得患者接受例如约2至约20或例如约6个剂量的IRAK4通路抑制剂)。可以施用较高的初始负荷剂量,然后是一个或多个较低的剂量。然而,其他剂量方案可能是有用的。通过常规技术和测定法很容易监测该疗法的进展。

[0238] IRAK4通路抑制剂可以通过任何合适的方式施用,包括口服、肠胃外、局部、皮下、腹膜内、肺内、鼻内和/或病灶内施用。肠胃外输注包括肌内、静脉内、动脉内、腹膜内或皮下施用。还考虑鞘内施用。另外,IRAK4通路抑制剂可以适当地通过脉冲输注施用,例如以递减剂量的IRAK4通路抑制剂施用。

[0239] 如果提供多个剂量的IRAK4通路抑制剂,则可以使用相同或不同的施用方式来提供每个剂量。在一个实施方案中,通过口服施用每种剂量。例如,可以片剂形式提供一种或多种IRAK4通路抑制剂。例如,可以每天施用两次一种或多种IRAK4通路抑制剂。在另一个实施方案中,每次暴露都是静脉内(i.v.)给予的。在另一个实施方案中,每次暴露通过皮下(s.c.)施用给予。在又一个实施方案中,暴露是通过静脉内和皮下施用二者给予。

[0240] 2.组合疗法

[0241] 该方法可以进一步包括将有效量的IRAK4通路抑制剂与其他治疗剂组合施用于患者。在某些情况下,其他治疗剂是另外的IRAK4通路抑制剂。在某些情况下,其他治疗剂是皮质类固醇、非甾体抗炎药(NSAID)、氯喹、羟基氯喹(PLAQUENIL®)、环孢霉素、咪唑硫嘌呤、甲氨蝶呤、霉酚酸酯(CELLCEPT®)或环磷酰胺(CYTOXAN®)。在某些情况下,IRAK4通路抑制剂可与手术组合使用。

[0242] 组合疗法可以提供“协同作用”并证明是“协同的”,即,当活性成分一起使用时所达到的效果大于单独使用化合物所产生的效果之和。当活性成分是以下时可以获得协同作用:(1)在组合的单位剂量制剂中共同配制和施用或同时递送;(2)作为单独的制剂交替或平行递送;或(3)通过其他一些方案。当以交替疗法递送时,当顺序施用或递送化合物时,可获得协同作用。通常,在交替疗法期间,顺序(即,依次)施用有效剂量的每种活性成分,而在组合疗法中,一起施用有效剂量的两种或更多种活性成分。

[0243] 如上所述,治疗方法可包括施用两种或更多种(例如三种或更多种)IRAK4通路抑制剂的组合。在某些情况下,例如,组合(或者顺序或者伴随地)施用两种IRAK4抑制剂。在一些情况下,例如,组合(或者顺序或者伴随地)施用两种IRAK1抑制剂。在某些情况下,例如,组合(或者顺序或者伴随地)施用两种TLR抑制剂。在某些情况下,例如,组合(或者顺序或者伴随地)施用两种IL-1R抑制剂。在一些情况下,例如,组合(或者顺序或者伴随地)施用两种IL-33R抑制剂。在某些情况下,例如,组合(或者顺序或者伴随地)施用两种MyD88抑制剂。

[0244] 通常，为了预防或治疗疾病，其他治疗剂的适当剂量将取决于待治疗疾病的类型、抗体类型、疾病的严重程度和病程、IRAK4通路抑制剂和其他药剂(例如皮质类固醇)是用于预防还是治疗目的施用、先前的治疗、患者的临床病史以及对IRAK4通路抑制剂和其他药剂的反应以及主治医师的判断。IRAK4通路抑制剂和其他药剂适当地一次或通过一系列治疗施用于患者。IRAK4通路抑制剂通常如上所述进行施用。根据疾病的类型和严重程度，约20mg/m^2至600mg/m^2的其他药剂是用于施用于患者的初始候选剂量，例如，无论是通过一次或多次单独施用，或通过连续输注。一种典型的日剂量范围可以为约20mg/m^2、85mg/m^2、90mg/m^2、125mg/m^2、200mg/m^2、400mg/m^2、500mg/m^2或更高，这取决于上述因素。对于几天或更长时间的重复施用，根据状况，持续治疗直至出现期望的疾病症状抑制。因此，可以向患者施用约20mg/m^2、85mg/m^2、90mg/m^2、125mg/m^2、200mg/m^2、400mg/m^2、500mg/m^2、600mg/m^2(或其任何组合)中的一个或多个剂量。这样的剂量可以例如每周或每两周、三周、四周、五或六周间歇地施用(例如，使得患者接受约两个至约二十个剂量，例如约六个剂量的其他药剂)。可以施用较高的初始负荷剂量，然后施用一个或多个较低的剂量。然而，其他剂量方案可能是有用的。通过常规技术和测定法很容易监测该疗法的进展。

[0245] 在一个实施方案中，患者先前从未施用过任何药物来治疗IRAK4介导的疾患或病症。在另一个实施方案中，患者先前已经施用一种或多种药物来治疗IRAK4介导的疾患或病症。在另一个实施方案中，患者对先前已经施用的治疗IRAK4介导的疾患或病症的一种或多种药物没有反应。受试者可能对其无反应的此类药物包括，例如，皮质类固醇、非类固醇抗炎药(NSAID)、氯喹、羟基氯喹(PLAQUENIL®)、环孢霉素、咪唑硫嘌呤、甲氨蝶呤、霉酚酸酯(CELLCEPT®)和/或环磷酰胺(CYTOXAN®)，其没有与IRAK4通路抑制剂组合施用。

[0246] VI.诊断试剂盒和组合物

[0247] 本发明进一步提供了诊断试剂盒和组合物，其包含一种或多种试剂(例如，多肽[如抗体或其抗原结合片段]或多核苷酸[如探针或引物])，用于测定患有IRAK4介导的疾患或病症(例如，免疫疾患、炎性疾患、纤维化疾患、嗜酸性细胞疾患、感染、疼痛、中枢神经系统疾患、急性肾脏损伤、慢性肾脏疾病、子宫内膜异位症、非酒精性脂肪肝疾病、代谢综合征和肥胖症)的个体或患者的样品中表1中列出的一个或多个基因(例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或所有24个基因)的表达水平。在一些情况下，表1中列出的一个或多个基因的表达水平相对于参考表达水平增加，鉴定患有IRAK4介导的疾患或病症的患者可受益于包括IRAK4通路抑制剂的治疗。在其他情况下，表1中列出的一个或多个基因的表达水平相对于参考表达水平降低，鉴定患有IRAK4介导的疾患或病症的患者可受益于包括IRAK4通路抑制剂的治疗。任选地，试剂盒可进一步包括使用该试剂盒来鉴定具有更高的受益于IRAK4通路抑制剂治疗的可能性的患者的说明书。在另一种情况下，如果患者未接受过治疗，并且相对于参考表达水平，表1中列出的一个或多个基因的表达水平增加，试剂盒可进一步包括使用该试剂盒选择用于治疗患有IRAK4介导的疾患或病症的患者的药物的说明书，所述药物例如，包含IRAK4通路抑制剂的药物，所述IRAK4通路抑制剂如IRAK4抑制剂、IRAK1抑制剂、toll样受体(TLR)抑制剂、白介素-1受体(IL-1R)抑制剂、白介素-33受体(IL-33R)抑制剂或髓样分化主要反应基因88(MyD88)抑制剂或其组合。

在另一种情况下,如果患者在接受第一剂量的包含IRAK4通路抑制剂的治疗后,相对于参考表达水平,表1中列出的一个或多个基因的表达水平降低,试剂盒可进一步包括使用该试剂盒选择用于治疗患有IRAK4介导的疾患或病症的患者的药物的说明书,所述药物例如包含IRAK4通路抑制剂的药物,如IRAK4抑制剂、IRAK1抑制剂、toll样受体(TLR)抑制剂、白介素-1受体(IL-1R)抑制剂、白介素-33受体(IL-33R)抑制剂或髓样分化主要反应基因88(MyD88)抑制剂或其组合。

[0248] 本发明的组合物包括能够测定RNASE4和任选地一种或多种其他生物标志物(例如,PSA和/或ANG)的表达水平的多肽(例如,抗体或其抗原结合片段)或多核苷酸(例如,探针和/或引物)。

[0249] 实施例

[0250] 提供以下实施例说明但不限制本发明。

[0251] 实施例1.鉴定IRAK4缺陷患者中对TLR7/8刺激反应受损的基因

[0252] 为了确定可用作药效和预测生物标志物的候选IRAK4生物标志物基因,首先鉴定了与健康患者相比,携带IRAK4功能丧失突变的患者中,TLR刺激后显示诱导显著降低的基因。为此,进行了GEO登录号GSE25742的微阵列数据集(Alsina等人Nat.Immunol.15:1134-42,2014)的分析,该数据集为来自患有Toll样受体(TLR)和白介素-1受体(IL-1R)(即Toll/IL-1受体(TIR)通路)信号传导缺陷的患者的全血的全基因组微阵列表达谱的研究。对微阵列数据集的分析确定了285个基因,这些基因显示与健康患者对照相比,来自IRAK4缺陷患者的全血中TLR7/8刺激剂R848(瑞喹莫德)的诱导显著降低(伪发现率(FDR)<0.05;倍数变化(FC)>1.25)(图1A-1B和6)。尽管发现健康患者对照响应R848上调I型干扰素(IFN),但是IRAK4$^{-/-}$患者未能响应R848上调I型IFN和其他TLR调控的基因(图2)。

[0253] 实施例2鉴定系统性红斑狼疮(SLE)患者中上调的基因

[0254] 进行了两个肾外系统性红斑狼疮(SLE)患者组的分析,以确定实施例1中鉴定的285个差异表达基因中的哪些也在SLE患者中显示提高的基线表达。分析了外周血单个核细胞(PBMC)微阵列数据(密歇根大学组;SLE(n=61),健康对照(HC)(n=20))和全血RNA测序数据(ROSE II期研究(Kalunian等人Ann.Rheum.Dis.75:196-202,2016);SLE(n=103),HC(n=19))的两个数据集在SLE和HC组之间的差异表达。随后在这两个数据集中,鉴定出与健康患者相比,285个差异表达的基因中在SLE患者中有44个基因上调(p<0.05;FC>1.2)(图3和6)。

[0255] 实施例3.使用IRAK4激酶缺失小鼠表征IRAK4通路基因。

[0256] 产生IRAK4激酶缺失(KD)小鼠以进一步表征实施例2中鉴定的推定IRAK4通路基因。使用小鼠IRAK4互补DNA的5'端作为探针,从129/J小鼠基因组文库中分离出IRAK4的基因组DNA。使用标准克隆技术,设计靶向构建体以破坏ATG起始密码子,并用PGK-Neo盒替代IRAK4基因的外显子2的一部分。将靶向质粒线性化并转染至129/Ola背景的胚胎干细胞(E14克隆)中。将同源重组的胚胎干细胞系注射到3.5天的C57BL/6J(B6)胚泡中,随后将其转移到CD1假孕寄养母体内以产生嵌合后代。将雄性嵌合体与C57BL/6J雌性回交以产生刺鼠后代。通过Southern印迹分析验证了F1杂合子代中的种系传递,并杂交F1杂合子以获得纯合突变小鼠。

[0257] 收获来自IRAK4 KD小鼠(n=5)和野生型对照小鼠(n=5)的骨髓源巨噬细胞

(BMDM)，并用TLR7激动剂R848体外刺激四个小时。通过Fluidigm进行基因表达分析，分析来自IRAK4 KD和野生型对照小鼠的未刺激和刺激的BMDM中推定IRAK4通路生物标志物基因。基因表达分析表明，与IRAK4野生型小鼠相比，来自IRAK4 KD小鼠的BMDM中，推定IRAK4通路生物标志物基因显示TLR7诱导的受损诱导(图4和6)。来自人IRAK4$^{-/-}$患者全血的类似基因表达分析表明，某些推定IRAK4通路生物标志物基因也显示出TLR7诱导的受损诱导(图6)。特别地，发现总共44个推定IRAK通路生物标志物基因中的24个基因在人和小鼠中均显示出TLR7诱导的受损诱导。这些24个IRAK4通路生物标志物列于表1中，并在本文中进行了描述，突出了人与小鼠系统之间的共性。

[0258] 其他基因表达分析表明，与IRAK4野生型小鼠相比，IFNβ1在IRAK4 KD小鼠中显示出较低的R848诱导($p=0.02$)(图5)。与IRAK4野生型小鼠相比，在IRAK4 KD小鼠中其他IFN调控基因(OAS1A、OAS2、IFIT1、IFNA5和MX1)显示出相同趋势，即R848诱导的降低($p<0.15$)(图7A-7E)。

[0259] 实施例4.IRAK4小分子抑制剂对IRAK4通路生物标志物基因的剂量依赖性下调。

[0260] 随后在人全血样品中，基于R848的诱导性和两种不同IRAK4小分子抑制剂测试化合物G03074387(G-4387)(BMS)和G03081557(G-1557)(Pfizer)的剂量依赖性下调，表征了24个IRAK4通路生物标志物基因。来自三名健康供体的全血样品被分为六组：(1)未刺激；(2)用1.25μM(～440ng/ml)的R848刺激；(3)G-4387在IC50(268nM)下持续1小时+R848刺激3.5小时；(4)G-4387在IC70(553nM)下持续1小时+R848刺激3.5小时；(5)G-4387在IC90(1.75μM)下持续1小时+R848刺激3.5小时；(6)G-4387在5μM下持续1小时+R848刺激3.5小时。使用来自相同三个健康供体的全血样品对G-1557进行了类似的实验，不同的是，第(3)-(6)组中G-1557的剂量如下：(3)G-1557，IC50(13nM)；(4)G-1557，IC70(25nM)；(5)G-1557，IC90(70nM)；和(6)G-1557，200nM。对于这两个实验，随后都提取了RNA，并通过qPCR测量了24个IRAK4通路生物标志物基因的转录水平。这些实验的结果示于图8和9中。在24个IRAK4通路生物标志物基因中，全血中的9个基因(CD38、SOCS3、AQP9、CDKN1A、GADD45B、B4GALT5、IL15RA、TNFAIP3和SOCS1)被G-4387和G-1557剂量依赖性下调(图9)。此外，在上述实施例2中描述的ROSE II期和密歇根大学SLE组中，针对这些IRAK4生物标志物基因，在SLE患者血液中观察到相互关联的特征(图10A-10B)。还在IRAK4通路生物标志物基因和干扰素标记度量(ISM)和抗dsDNA状态以及BAFF、抗RNP抗体和抗Sm抗体水平之间观察到显著的正相关。在两个SLE数据集中的IRAK4生物标志物基因和补体成分3(C3)和补体成分4(C4)的水平之间观察到显著的负相关性。

[0261] 总之，数据表明这些IRAK4调控基因的协调表达反映了TLR和其他上游刺激，因此反映了IRAK通路活性，从而支持已鉴定的IRAK4通路生物标志物基因作为药效学和预测诊断的生物标志物，用于可能对包括IRAK4通路抑制剂(例如IRAK4小分子抑制剂)的治疗反应的患者。

[0262] 其他实施方案

[0263] 尽管出于清楚理解的目的已经通过说明和实施例的方式详细地描述了前述发明，但是这些描述和实施例不应解释为限制本发明的范围。本文引用的所有专利和科学文献的公开内容明确地全文引入作为参考。

序列表

<110> 豪夫迈·罗氏有限公司

<120> IRAK4介导的疾患和病症的诊断和治疗方法

<130> 50474-170WO2

<150> US 62/521,299
<151> 2017-06-16

<160> 48

<170> PatentIn version 3.5

<210> 1
<211> 5694
<212> RNA
<213> 智人

<400> 1

[0001]

gaggcaaggg guugggggug ggaagggaaa cagagaaaag gcaagugaaa cagaagggga 60

ggugcaguuu cagaacccag ccagccucuc ucuugcugcc uagccuccug ccggccucau 120

cuucgcccag ccaaccccgc cuggagcccu auggccaacu gcgaguucag cccggugucc 180

ggggacaaac ccugcugccg gcucucuagg agagcccaac ucugucuugg cgucaguauc 240

cuggcccuga uccucgucgu ggugcucgcg guggucgucc cgagguggcg ccagcagugg 300

agcggcccgg gcaccaccaa gcgcuuuccc gagaccgucc uggcgcgaug cgucaaguac 360

acugaaauuc auccugagau gagacaugua gacugccaaa guguauggga ugcuuucaag 420

ggugcauuua uuucaaaaca uccuugcaac auuacugaag aagacuauca gccacuaaug 480

aaguugggaa cucagaccgu accuugcaac aagauucuuc uuuggagcag aauaaaagau 540

cuggcccauc aguucacaca gguccagcgg gacauguuca cccuggagga cacgcugcua 600

ggcuaccuug cugaugaccu cacauggugu ggugaauuca acacuuccaa aauaaacuau 660

caaucuugcc cagacuggag aaaggacugc agcaacaacc cuguuucagu auucuggaaa 720

acgguuuccc gcagguuugc agaagcugcc ugugaugugg uccaugugau gcucaaugga 780

ucccgcagua aaaucuuuga caaaaacagc acuuuuggga guguggaagu ccauaauuug 840

caaccagaga agguucagac acuagaggcc ugggugauac augguggaag agaagauucc 900

agagacuuau gccaggaucc caccauaaaa gagcuggaau cgauuauaag caaaaggaau 960

auucaauuuu ccugcaagaa uaucuacaga ccugacaagu uucuucagug ugugaaaaau 1020

ccugaggauu caucuugcac aucugagauc ugagccaguc gcugugguug uuuuagcucc 1080

uugacuccuu gugguuuaug ucaucauaca ugacucagca uaccugcugg ugcagagcug 1140

aagauuuugg aggguccucc acaauaaggu caaugccaga gacggaagcc uuuuucccca 1200

aagucuuaaa auaacuuaua ucaucagcau accuuuauug ugaucuauca auagucaaga 1260

aaaauuauug uauaagauua gaaugaaaau uguauguuaa guuacuucac uuuaauucuc 1320

augugauccu uuuauguuau uuauauauug guaacauccu uucuauugaa aaaucaccac 1380

[0002]

accaaaccuc ucuuauuaga acaggcaagu gaagaaaagu gaaugcucaa guuuuucaga 1440

aagcauuaca uuuccaaaug aaugaccuug uugcaugaug uauuuuugua cccuuccuac 1500

agauagucaa accauaaacu ucauggucau gggucauguu ggugaaaauu auucuguagg 1560

auauaagcua cccacguacu uggugcuuua ccccaacccu uccaacagug cugugagguu 1620

gguauuauuu cauuuuuuag augagaaaau gggagcucag agagguuaua uauuuaaguu 1680

ggugcaaaag uaauugcaag uuuugccacc gaaaggaaug gcaaaaccac aauuauuuuu 1740

gaaccaaccu aauaauuuac cguaaguccu acauuuagua ucaagcuaga gacugaauuu 1800

gaacucaacu cuguccaacu ccaaaauuca ugugcuuuuu ccuucuaggc cuuucauacc 1860

aaacuaauag uaguuuauau ucucuuccaa caaaugcaua uuggauuaaa uugacuagaa 1920

uggaaucugg aauauaguuc uucuggaugg cuccaaaaca cauguuuuuc uucccccguc 1980

uuccuccucc ucuucaugcu caguguuuua uauauguagu auacaguuaa aauauacuug 2040

uugcugguac uggcagcuua uauuuucucu cuuuuuucau ggauuaaccu ugcuugaggg 2100

cuuuaacaau uguauuacuu uuucaaagaa cuaagcuuua gcuucauuga uuuuuuucua 2160

uuuaauuggg uuuugcucuu cucuuuagca uuggaaacau agaaaugcuu ucugauuucu 2220

uuggguagau uuacguauuc agcuucuuga gauggaaguu uagaucacug auccuucagc 2280

uuguuuucuu uuuuguauac auagauuuua ggacgauaua uuuucccuug aguucugcuu 2340

uagcugcagc ucuuauguuu ugauaugccu cucuuuauua uccuucaguu aaaaauaucu 2400

uucaauucau uguuauauaa aaauaugugc cuaguuuuua acaucuggag auuuucuagu 2460

uuugaaaaaa acauaagcca ggcauggugg cucacaccug uauccccagc acuuugggag 2520

gccgagacgg gaggaucgcc ugagcucagg aguuuuuaca ccagccuggg aauaacagug 2580

agacauuauc uccaaaaaaa uuaccugggu augguguugu gcaccuguag ucccagcuac 2640

ucuggagacu gaggugggag gauuguuuga gcuugggagg uugaggcugc agggagcugu 2700

[0003]

gaucacacca cugcacucug gccugaguga cagauugaga cccugucuca auaaaagcaa 2760

aaauaaagaa aauaaaccau auguguugaa caaaggauua auaaaauuaau uugagacucc 2820

uucagggaau gaccacaauu uauugaaaau agccuaaaug uuggagucag gcauuucugg 2880

auucauauuu ugacaucaug cugucaucuu gaacaaaaug ccuaaccuuu cugaacuuca 2940

acuuccuugc cacucaaaua aggauuacaa aacuuaaaau gugguaagua cuaaagacga 3000

cagcaaaaau ugaguccagc acagagcuuc cuaaauaagc aagcacucaa cagaguuggu 3060

uccuuucuuc cucccugcu ugacaaucca guuucccaca ggagccuuug uagcuguagc 3120

caccaugguc aguccaggga uucuucacua gccccuucuc cccuggcaga cauccuugug 3180

ggaguuuagu cuuggcucga caugaggaug gggguuuggg accaguucug agugagaauc 3240

agacuugccc caaguugcca uuagcucccc cugcagaaug ucuucagaau cggggcccgg 3300

ucagucuccu gggugaccug cuguuuuccu cuuaagaucc uuuccacuuu gguugcugcu 3360

uucgggacuc aucgaguccu ugcucaacag gauaccccuu gaaguggcug ccugggccac 3420

aucccccuucc aaacaagaaa ucaaaauauu agaaaucaau uuuugaaauu uccccuagga 3480

agacucauuu gaguguucaa guucagagcc aguggagacc uuaggggagg guggucacaa 3540

ggauuuugca cagugcuuua gaggguccca gggagccaca gaggugguga ggggcugggu 3600

gcucuuuucu ccgugcauga ccuugugugu cuaucuucau uaccacaaug ccucaucucu 3660

accuccuuuc ccccuguagu uccaacgugg guaucuuugc caucucuggc ccgaaggacu 3720

uucugaccua cauguauaaa uacccccuca caauauauau uacuuuuccu auaagugacu 3780

ucucuacugg auuacugguu gcucauacac cucauauuuu acucguaaau cuacuacucc 3840

cugucugccu acuccauucu cauuugcugu agaaaauucu cuuaccaucc caacuuucac 3900

ccaccaucau gcuuacccaa aggcuguggg aaugaccugg gcccuaaugc cccuuuucua 3960

aauuccuaag gcucaccauu uuccuauugu aaugguucuu gaccuuauaa uguuugaggc 4020

[0004]

accuuuucaa auauaguccu uugauuucag acugaauacu ugaaaggaca cacacacaca 4080

uacguaagug cauaugacug cauacaccca cacacacaca cgugccugua uacagucaua 4140

ugauacauac acaaacacac gcacacaagc cugcauacau cauaugccaa caguggggau 4200

auguucugag aaaugcauca uuagaugauu uugucauugu gugaacauca uagaguguac 4260

uuacacuaac cuagaugguc uaaccuacua cacacccagg cuacauggua ucaccuauuc 4320

cuccuaggcu acaagccugu acagcgugug ucuguacuaa augcuguggg caauuuuaac 4380

cugaugguaa auguuugugu aucuaaacau aucuaaacau agaaaaggua caguaaacau 4440

gcaguauuau aaucuuauga gaccgucauc auauaugugg uccacuguuu gggccaucau 4500

uggcugaaaa gugguuaugc gacacaugac uguauauaua cuuuccuguu acaacaacag 4560

ugucucucaa uccacaguaa uugcagcauc caguaggucu uacuuuagcc cugagucacc 4620

auuuguguca acguguuuag ugccaugucc acgucucuca uguaacuggc agagcuauca 4680

aauauuuugg caaaacacau uguuucuuug gcuuugccuu gguaacuuuc ugugccuuuu 4740

guagcucuug uuuggaagaa gcucaaccca ugucugcaca cugugauaca agggggacag 4800

caucgacauc gacuuacuuc uuggugccuu auuccuccuu agaacaauuc cuaaaucugu 4860

aacuuaaguu ucucaggaag auuccauacu gcacagaaaa cugcuuuugu ggguuuuuaa 4920

aaggcaaguu guuauaugug cuggauaguu uuuaaguaug acauaaaaau uguauaaagu 4980

aaaauauuaa aauacaccua gaauacugua uaacuuuaag ucauuuuauc aacacauugc 5040

uaauccagau auuuucccgc aguuuuucuu ugaauaacag agcaauuaau uuacuuuuac 5100

uaugaagagu caucauuuua guauguauuu uaagcaaucc accaagaacu caguaggcag 5160

cugagaggug cugcccagag aaguggugau uagcuuggcc uuagcucacc cacacaaagc 5220

acaacaggcu uugaacuauu cccuaacggg gcauuuauuc uuuuuuuuuu uuuuuuuugg 5280

gagacggagu cucgcugucg cccaggcuag agugcagugg cgcgaucucg gcucacugca 5340

[0005]

ggcuccaccc ccuggggguc acgccauucu ccugccucag ccucccaagu agcugggacu 5400

gcaggcgccc gccaucucgc ccggcuaauu uuuuguauuu uuaguagaga cgggguuuca 5460

ccguguuagc caggauaggg cauuuauucu ugaacuugau ucagagaggc acacauuacc 5520

auucucuaau cagaaugcaa guagcgcaag gcgguggaaa cuauggaauu cggaggcagg 5580

ugaugcauug ggcgaguuua uuaacaucug ugacucucua guuugaaauu uauuuguaac 5640

agacaaaaau gaauuaaaca aacaauaaaa guauaauaaa gaacugugcu gaau 5694

<210> 2
<211> 300
<212> PRT
<213> 智人

<400> 2

Met Ala Asn Cys Glu Phe Ser Pro Val Ser Gly Asp Lys Pro Cys Cys
1 5 10 15

Arg Leu Ser Arg Arg Ala Gln Leu Cys Leu Gly Val Ser Ile Leu Val
20 25 30

Leu Ile Leu Val Val Val Leu Ala Val Val Val Pro Arg Trp Arg Gln
35 40 45

Gln Trp Ser Gly Pro Gly Thr Thr Lys Arg Phe Pro Glu Thr Val Leu
50 55 60

Ala Arg Cys Val Lys Tyr Thr Glu Ile His Pro Glu Met Arg His Val
65 70 75 80

Asp Cys Gln Ser Val Trp Asp Ala Phe Lys Gly Ala Phe Ile Ser Lys
85 90 95

His Pro Cys Asn Ile Thr Glu Glu Asp Tyr Gln Pro Leu Met Lys Leu
100 105 110

Gly Thr Gln Thr Val Pro Cys Asn Lys Ile Leu Leu Trp Ser Arg Ile
115 120 125

[0006] Lys Asp Leu Ala His Gln Phe Thr Gln Val Gln Arg Asp Met Phe Thr
130 135 140

Leu Glu Asp Thr Leu Leu Gly Tyr Leu Ala Asp Asp Leu Thr Trp Cys
145 150 155 160

Gly Glu Phe Asn Thr Ser Lys Ile Asn Tyr Gln Ser Cys Pro Asp Trp
165 170 175

Arg Lys Asp Cys Ser Asn Asn Pro Val Ser Val Phe Trp Lys Thr Val
180 185 190

Ser Arg Arg Phe Ala Glu Ala Ala Cys Asp Val Val His Val Met Leu
195 200 205

Asn Gly Ser Arg Ser Lys Ile Phe Asp Lys Asn Ser Thr Phe Gly Ser
210 215 220

Val Glu Val His Asn Leu Gln Pro Glu Lys Val Gln Thr Leu Glu Ala
225 230 235 240

Trp Val Ile His Gly Gly Arg Glu Asp Ser Arg Asp Leu Cys Gln Asp

245 250 255

Pro Thr Ile Lys Glu Leu Glu Ser Ile Ile Ser Lys Arg Asn Ile Gln
260 265 270

Phe Ser Cys Lys Asn Ile Tyr Arg Pro Asp Lys Phe Leu Gln Cys Val
275 280 285

Lys Asn Pro Glu Asp Ser Ser Cys Thr Ser Glu Ile
290 295 300

<210> 3
<211> 2737
<212> RNA
<213> 智人

<400> 3

[0007]

gcggcuccga cuuggacucc cugcuccgcu gcugccgcuu cggccccgca cgcagccagc 60

cgccagccgc ccgcccggcc cagcucccgc cgcggccccu ugccgcgguc ccucuccugg 120

ucccccucccg guugguccgg gggugcgcag ggggcagggc gggcgcccag gggaagcucg 180

agggacgcgc gcgcgaaggc uccuuugugg acuucacggc cgccaacauc ugggcgcagc 240

gcgggccacc gcuggccguc ucgccgccgc gucgccuugg ggacccgagg gggcucagcc 300

ccaaggacgg agacuucgau ucgggaccag ccccccggga ugcgguagcg gccgcugugc 360

ggaggccgcg aagcagcugc agccgccgcc gcgcagaucc acgcuggcuc cgugcgccau 420

ggucacccac agcaaguuuc ccgccgccgg gaugagccgc ccccuggaca ccagccugcg 480

ccucaagacc uucagcucca agagcgagua ccagcuggug gugaacgcag ugcgcaagcu 540

gcaggagagc ggcuucuacu ggagcgcagu gaccggcggc gaggcgaacc ugcugcucag 600

ugccgagccc gccggcaccu uucugauccg cgacagcucg gaccagcgcc acuucuucac 660

gcucagcguc aagacccagu cugggaccaa gaaccugcgc auccagugug agggggggcag 720

cuucucucug cagagcgauc cccggagcac gcagcccgug ccccgcuucg acugcgugcu 780

caagcuggug caccacuaca ugccgccccc uggagccccc uccuuccccu cgccaccuac 840

ugaacccucc uccgaggugc ccgagcagcc gucugcccag ccacucccug ggagucccc 900

cagaagagcc uauuacaucu acuccggggg cgagaagauc ccccuggugu ugagccggcc 960

ccucuccucc aacguggcca cucuucagca ucucugucgg aagaccguca acggccaccu 1020

ggacuccuau gagaaaguca cccagcugcc ggggcccauu cgggaguucc uggaccagua 1080

cgaugccccg cuuuaagggg uaaagggcgc aaagggcaug ggucgggaga ggggacgcag 1140

gccccucucc uccguggcac auggcacaag cacaagaagc caaccaggag agaguccugu 1200

agcucugggg ggaaagaggg cggacaggcc ccucccucug cccucucccu gcagaaugug 1260

gcaggcggac cuggaaugug uuggagggaa gggggaguac caccugaguc uccagcuucu 1320

ccggaggagc cagcuguccu ggugggacga uagcaaccac aaguggauuc uccuucaauu 1380

ccucagcuuc cccucugccu ccaaacaggg gacacuucgg gaaugcugaa cuaaugagaa 1440

cugccaggga aucuucaaac uuuccaacgg aacuuguuug cucuuugauu ugguuuaaac 1500

[0008]

cugagcuggu uguggagccu gggaaaggug gaagagagag agguccugag ggccccaggg 1560

cugcgggcug gcgaaggaaa uggucacacc ccccgcccac cccaggcgag gauccuggug 1620

acaugcuccu cucccuggcu ccggggagaa gggcuuuggg ugaccugaag ggaaccaucc 1680

ugguacccca cauccucucc uccgggacag ucaccgaaaa cacagguucc aaagucuacc 1740

uggugccuga gagcccaggg cccuuccucc guuuuaaggg ggaagcaaca uuuggagggg 1800

auggaugggc uggucagcug gucuccuuuu ccuacucaua cuauaccuuc cuguaccugg 1860

guggauggag cgggaggaug gaggagacgg gacaucuuuc accucaggcu ccugguagag 1920

aagacagggg auucuacucu gugccuccug acuaugucug gcuaagagau ucgccuuaaa 1980

ugcucccugu cccauggaga gggacccagc auaggaaagc cacauacuca gccuggaugg 2040

guggagaggc ugagggacuc acuggagggc accaagccag cccacagcca gggaaguggg 2100

gagggggggc ggaaacccau gccucccagc ugagcacugg gaaugucagc ccaguaagua 2160

uuggccaguc aggcgccucg uggucagagc agagccacca ggucccacug ccccgagccc 2220

ugcacagccc ucccuccugc cugggugggg gaggcuggag gucauuggag aggcuggacu 2280

gcugccaccc cgggugcucc cgcucugcca uagcacugau cagugacaau uuacaggaau 2340

guagcagcga uggaauuacc uggaacaguu uuuuguuuuu guuuuuguuu uuguuuuugu 2400

gggggggggc aacuaaacaa acacaaagua uucuguguca gguauugggc uggacagggc 2460

aguugugugu uggggugguu uuuuucucua uuuuuuuguu uguuucuugu uuuuuaauaa 2520

uguuuacaau cugccucaau cacucugucu uuuauaaaga uuccaccucc aguccucucu 2580

ccuccccccu acucaggccc uugaggcuau uaggagaugc uugaagaacu caacaaaauc 2640

ccaauccaag ucaaacuuug cacauauuua uauuuauauu cagaaaagaa acauuucagu 2700

aauuuauaau aaagagcacu auuuuuuaau gaaaaac 2737

<210> 4

[0009] <211> 225

<212> PRT

<213> 智人

<400> 4

Met Val Thr His Ser Lys Phe Pro Ala Ala Gly Met Ser Arg Pro Leu
1 5 10 15

Asp Thr Ser Leu Arg Leu Lys Thr Phe Ser Ser Lys Ser Glu Tyr Gln
20 25 30

Leu Val Val Asn Ala Val Arg Lys Leu Gln Glu Ser Gly Phe Tyr Trp
35 40 45

Ser Ala Val Thr Gly Gly Glu Ala Asn Leu Leu Leu Ser Ala Glu Pro
50 55 60

Ala Gly Thr Phe Leu Ile Arg Asp Ser Ser Asp Gln Arg His Phe Phe
65 70 75 80

Thr Leu Ser Val Lys Thr Gln Ser Gly Thr Lys Asn Leu Arg Ile Gln

85 90 95

Cys Glu Gly Gly Ser Phe Ser Leu Gln Ser Asp Pro Arg Ser Thr Gln
100 105 110

Pro Val Pro Arg Phe Asp Cys Val Leu Lys Leu Val His His Tyr Met
115 120 125

Pro Pro Pro Gly Ala Pro Ser Phe Pro Ser Pro Pro Thr Glu Pro Ser
130 135 140

Ser Glu Val Pro Glu Gln Pro Ser Ala Gln Pro Leu Pro Gly Ser Pro
145 150 155 160

Pro Arg Arg Ala Tyr Tyr Ile Tyr Ser Gly Gly Glu Lys Ile Pro Leu
165 170 175

Val Leu Ser Arg Pro Leu Ser Ser Asn Val Ala Thr Leu Gln His Leu
180 185 190

Cys Arg Lys Thr Val Asn Gly His Leu Asp Ser Tyr Glu Lys Val Thr
195 200 205

[0010]

Gln Leu Pro Gly Pro Ile Arg Glu Phe Leu Asp Gln Tyr Asp Ala Pro
210 215 220

Leu
225

<210> 5
<211> 3031
<212> RNA
<213> 智人

<400> 5
acugugauuu ggcaacacaa cuggcacauc ucuuuucuca ucucuugaaa aaaaccaaca 60

gagaaaaaag uaccuugaga auaaagguaa ugauuaaucu gucaggcaca aaagggauug 120

uuuuggggau uucggguucu aagucgcaga uucaaacaaa uagcagcgaa cagggaauga 180

caguuccacc agaagacgau uaagccacag ccucuaauug gaacggcauu uguacaguca 240

gagacucuua ccagacaucu ccaggaaucu gugagccauu gucaaaacgu ccauuuucau 300

cuggcuguga aagugaggac cacaacaggu agguauuggu agaaacagga guccucagag 360

aagccccaag augcagccug agggagcaga aaagggaaaa agcuucaagc agagacuggu 420

cuugaagagc agcuuagcga aagaaacccu cucugaguuc uugggcacgu ucaucuugau 480

uguccuugga uguggcugug uugcccaagc uauucucagu cgaggacguu uuggaggggu 540

caucacuauc aauguuggau uuucaauggc aguugcaaug gccauuuaug uggcuggcgg 600

ugucucuggu ggucacauca acccagcugu gucuuuagca augugucucu uuggacggau 660

gaaaugguuc aaauugccau uuuauguggg agcccaguuc uugggagccu uuguggggge 720

ugcaaccguc uuuggcauuu acuaugaugg acuuaugucc uuugcuggug gaaaacugcu 780

gaucguggga gaaaaugcaa cagcacacau uuuugcaaca uacccagcuc cguaucuauc 840

ucuggcgaac gcauuugcag aucaaguggu ggccaccaug auacuccuca uaaucgucuu 900

ugccaucuuu gacuccagaa acuugggagc ccccagaggc cuagagccca uugccaucgg 960

[0011]

ccuccugauu auugucauug cuuccucccu gggacugaac aguggcugug ccaugaaccc 1020

agcucgagac cugaguccca gacuuuucac ugccuuggca ggcugggggu uugaagucuu 1080

cagagcugga aacaacuucu gguggauucc uguagugggc ccuuugguug gugcugucau 1140

uggaggccuc aucuauguuc uugucauuga aauccaccau ccagagccug acucagucuu 1200

uaagacagaa caaucugagg acaaaccaga gaaauaugaa cucaguguca ucauguagug 1260

gcaugcucag cucuggauuu gcagucaguu ugggauucuc uucagaaaga uggcaucuaa 1320

gugucugugu ucuuguaagc cugaggugga auccacccag uuuugucugc uagccauaug 1380

ggacaucuaa uuggaaaagc aucugcauaa aaguuuggaa acaaugacca cuucucuacc 1440

auugucccce acccccaccc cccagaauaa cgcugacugu ccccugaaac agccuucucu 1500

ccugcccugu uuauuucauc cucgauggga auucuugcua gguaagcacu aauaacucgg 1560

caucuugacg auagucccau uugggugguu ucagcugcac uaucuguaug aaaugguguc 1620

accaaaaccc uuuucuucag uaucgacaaa gauuacauuc ugaguaccaa ccaaacccua 1680

aauugaaaga caaaacuaug guuucaguca acauauucau gaauuaggga gcuaaugggu 1740

uaagcuucca guucccgcua ugcuacugga uuuguauaaa uacugauauu cuccaaaccu 1800

agugguguag ggagcaagag aaugcagcug gaaggcacaa ggggaggaca uuguggcauu 1860

cagaaacugc aggagacaag augaauuuga gaagccaaau ggaauuuuua auggaaacca 1920

uuuaucagau uaaucucuug cucuccugca uuuuagagga caccaauuaa uuuccugguc 1980

uuuaguauau aauaaccuaa aauaccauug uaaccucagu caugaaaaau acaucacucu 2040

gucuuuuuag cucaaaugua uuuuccuaau ugcccacuug agaacagaca uuugacaagu 2100

uauaucaacg acugugcuug uccauuauuu uacacaugcc cuagaagcca aaacugaaag 2160

ccacuggauc cuggucuagc ugaaucuuca gagugggagg ucuccaaaaa gauauuaccu 2220

uauugggcuu aacaauucac aaggcacuuu cacacccauu aucuaauuua auccucauaa 2280

[0012]

ugacuaugug aggcaaaugc cacauugccc auuuuucaga uaaagaaaca aaaucuuagg 2340

gaagauaagu ugaguugucc aagagcacac ugaaaguuga auguuaucua augcauuccu 2400

cuaccuuuca gaagaucagu agcuggcuga caaucuuugc caaaucuucc uugcuagcca 2460

gaaguggaau uggcagcuuc uagaauaugu acaccucugg acaaaauguu ccucaaucuu 2520

aagauacaaa gacccucauu gucugggucu auucccacac uuacugagua cagaugaagg 2580

aaaagugguag caauuuaauc auaacuuuca uuugcugaaa aacauuauga gaaggccucc 2640

cuuccuaagc caccucuggu cuugcuaagu cuugaucuug cuuccugcca gcaccaaaca 2700

uuacauucag gggauuuccu cuggcucagu cuuuuccccu ugaaguucuc uaauagaugu 2760

uacuuuugac aaaagaucgc cuaugaguua caagcaccag gggaugcucu acaucaaggg 2820

augcaccuuc agucaaacug ucaaaaagcc cagaauuccc aaaggcauua gguuucccaa 2880

cugcuuugug cugauaucag aacagcagaa auuaaaugug aaauguuucu gaugacuuau 2940

guucuacaau cuauggacau acgggauuuu uuuuucuugc uuugaagcua ccuggauauu 3000

uccuauuuga aauaaaauug uucggucauu g 3031

<210> 6
<211> 295
<212> PRT
<213> 智人

<400> 6

Met Gln Pro Glu Gly Ala Glu Lys Gly Lys Ser Phe Lys Gln Arg Leu
1 5 10 15

Val Leu Lys Ser Ser Leu Ala Lys Glu Thr Leu Ser Glu Phe Leu Gly
20 25 30

Thr Phe Ile Leu Ile Val Leu Gly Cys Gly Cys Val Ala Gln Ala Ile
35 40 45

Leu Ser Arg Gly Arg Phe Gly Gly Val Ile Thr Ile Asn Val Gly Phe
[0013] 50 55 60

Ser Met Ala Val Ala Met Ala Ile Tyr Val Ala Gly Gly Val Ser Gly
65 70 75 80

Gly His Ile Asn Pro Ala Val Ser Leu Ala Met Cys Leu Phe Gly Arg
85 90 95

Met Lys Trp Phe Lys Leu Pro Phe Tyr Val Gly Ala Gln Phe Leu Gly
100 105 110

Ala Phe Val Gly Ala Ala Thr Val Phe Gly Ile Tyr Tyr Asp Gly Leu
115 120 125

Met Ser Phe Ala Gly Gly Lys Leu Leu Ile Val Gly Glu Asn Ala Thr
130 135 140

Ala His Ile Phe Ala Thr Tyr Pro Ala Pro Tyr Leu Ser Leu Ala Asn
145 150 155 160

Ala Phe Ala Asp Gln Val Val Ala Thr Met Ile Leu Leu Ile Ile Val
165 170 175

Phe Ala Ile Phe Asp Ser Arg Asn Leu Gly Ala Pro Arg Gly Leu Glu
180 185 190

Pro Ile Ala Ile Gly Leu Leu Ile Ile Val Ile Ala Ser Ser Leu Gly
195 200 205

Leu Asn Ser Gly Cys Ala Met Asn Pro Ala Arg Asp Leu Ser Pro Arg
210 215 220

Leu Phe Thr Ala Leu Ala Gly Trp Gly Phe Glu Val Phe Arg Ala Gly
225 230 235 240

Asn Asn Phe Trp Trp Ile Pro Val Val Gly Pro Leu Val Gly Ala Val
245 250 255

Ile Gly Gly Leu Ile Tyr Val Leu Val Ile Glu Ile His His Pro Glu
260 265 270

Pro Asp Ser Val Phe Lys Thr Glu Gln Ser Glu Asp Lys Pro Glu Lys
275 280 285

[0014] Tyr Glu Leu Ser Val Ile Met
290 295

<210> 7
<211> 2175
<212> RNA
<213> 智人

<400> 7
guuguauauc agggccgcgc ugagcugcgc cagcugaggu gugagcagcu gccgaaguca 60

guuccuugug gagccggagc ugggcgcgga uucgccgagg caccgaggca cucagaggag 120

gcgccauguc agaaccggcu ggggaugucc gucagaaccc augcggcagc aaggccugcc 180

gccgccucuu cggcccagug gacagcgagc agcugagccg cgacugugau gcgcuaaugg 240

cgggcugcau ccaggaggcc cgugagcgau ggaacuucga cuuugucacc gagacaccac 300

uggaggguga cuucgccugg gagcgugugc ggggccuugg ccugcccaag cucuaccuuc 360

ccacggggcc ccggcgaggc cgggaugagu ugggaggagg caggcggccu ggcaccucac 420

cugcucugcu gcaggggaca gcagaggaag accaugugga ccugucacug ucuuguaccc 480

uugugccucg cucaggggag caggcugaag ggucccccagg uggaccugga gacucucagg 540

gucgaaaacg gcggcagacc agcaugacag auuucuacca cuccaaacgc cggcugaucu 600

ucuccaagag gaagcccuaa uccgcccaca ggaagccugc aguccuggaa gcgcgagggc 660

cucaaaggcc cgcucuacau cuucugccuu agucucaguu ugugugucuu aauuauuauu 720

uguguuuuaa uuuaaaacacc uccucaugua cauacccugg ccgccccccug ccccccagcc 780

ucuggcauua gaauuauuua aacaaaaacu aggcgguuga augagagguu ccuaagagug 840

cugggcauuu uuauuuuaug aaauacuauu uaaagccucc ucaucccgug uucuccuuuu 900

ccucucuccc ggagguuggg ugggccggcu ucaugccagc uacuuccucc uccccacuug 960

uccgcugggu gguacccucu ggaggggugu ggcuccuucc caucgcuguc acaggcgguu 1020

augaaauuca cccccuuucc uggacacuca gaccugaauu cuuuuucauu ugagaaguaa 1080

[0015]

acagauggca cuuugaaggg gccucaccga gugggggcau caucaaaaac uuuggagucc 1140

ccucaccucc ucuaagguug ggcaggguga cccugaagug agcacagccu agggcugagc 1200

uggggaccug guacccuccu ggcucuugau acccccccucu gucuugugaa ggcaggggga 1260

aggugggguc cuggagcaga ccaccccgcc ugcccucaug gccccucuga ccugcacugg 1320

ggagcccguc ucaguguuga gccuuuuccc ucuuuggcuc cccuguaccu uuugaggagc 1380

cccagcuacc cuucuucucc agcugggcuc ugcaauuccc cucugcugcu gucccucccc 1440

cuuguccuuu cccuucagua cccucucagc uccagguggc ucugaggugc cugucccacc 1500

cccaccccca gcucaaugga cuggaagggg aagggacaca caagaagaag ggcacccuag 1560

uucuaccuca ggcagcucaa gcagcgaccg ccccccuccuc uagcuguggg ggugaggguc 1620

ccauguggug gcacaggccc ccuugagugg gguuaucucu guguuagggg uauaugaugg 1680

gggaguagau cuuucuagga gggagacacu ggccccucaa aucguccagc gaccuuccuc 1740

auccacccca ucccucccca guucauugca cuuugauuag cagcggaaca aggagucaga 1800

cauuuuaaga ugguggcagu agaggcuaug gacagggcau gccacguggg cucauauggg 1860

gcugggagua guugucuuuc cuggcacuaa cguugagccc cuggaggcac ugaagugcuu 1920

aguguacuug gaguauuggg gucugacccc aaacaccuuc cagcuccugu aacauacugg 1980

ccuggacugu uuucucucgg cucccccaugu guccugguuc ccguuucucc accuagacug 2040

uaaaccucuc gagggcaggg accacacccu guacuguucu gugucuuuca cagcuccucc 2100

cacaaugcug aauauacagc aggugcucaa uaaaugauuc uuagugacuu uacuuguaaa 2160

aaaaaaaaaa aaaaa 2175

<210> 8
<211> 164
<212> PRT
<213> 智人

[0016] <400> 8

Met Ser Glu Pro Ala Gly Asp Val Arg Gln Asn Pro Cys Gly Ser Lys
1 5 10 15

Ala Cys Arg Arg Leu Phe Gly Pro Val Asp Ser Glu Gln Leu Ser Arg
20 25 30

Asp Cys Asp Ala Leu Met Ala Gly Cys Ile Gln Glu Ala Arg Glu Arg
35 40 45

Trp Asn Phe Asp Phe Val Thr Glu Thr Pro Leu Glu Gly Asp Phe Ala
50 55 60

Trp Glu Arg Val Arg Gly Leu Gly Leu Pro Lys Leu Tyr Leu Pro Thr
65 70 75 80

Gly Pro Arg Arg Gly Arg Asp Glu Leu Gly Gly Gly Arg Arg Pro Gly
85 90 95

Thr Ser Pro Ala Leu Leu Gln Gly Thr Ala Glu Glu Asp His Val Asp
100 105 110

Leu Ser Leu Ser Cys Thr Leu Val Pro Arg Ser Gly Glu Gln Ala Glu
115 120 125

Gly Ser Pro Gly Gly Pro Gly Asp Ser Gln Gly Arg Lys Arg Arg Gln
130 135 140

Thr Ser Met Thr Asp Phe Tyr His Ser Lys Arg Arg Leu Ile Phe Ser
145 150 155 160

Lys Arg Lys Pro

<210> 9
<211> 1393
<212> RNA
<213> 智人

<400> 9

[0017]

ucagaucgcc gaagcgucgg acuaccguug guuuccgcaa cuuccuggau uauccucgcc 60

aaggacuuug caauauauuu uuccgccuuu ucuggaagga uuucgcugcu ucccgaaggu 120

cuuggacgag cgcucuagcu cugugggaag guuuugggcu cucuggcucg gauuuugcaa 180

uuucucccug gggacugccg uggagccgca uccacugugg auuauaauug caacaugacg 240

cuggaagagc ucguggcgug cgacaacgcg gcgcagaaga ugcagacggu gaccgccgcg 300

guggaggagc uuuuugguggc cgcucagcgc caggaucgcc ucacaguggg gguguacgag 360

ucggccaagu ugaugaaugu ggacccagac agcguggucc ucugccucuu ggccauugac 420

gaggaggagg aggaugacau cgcccugcaa auccacuuca cgcucaucca guccuucugc 480

ugugacaacg acaucaacau cgugcgggug ucgggcaugc agcgccuggc gcagcuccug 540

ggagagccgg ccgagaccca gggcaccacc gaggcccgag accugcauug ucuccugguc 600

acgaacccuc acacggacgc cuggaagagc cacggcuugg uggagguggc cagcuacugc 660

gaagaaagcc ggggcaacaa ccaguggguc cccuacaucu cucuucagga acgcugaggc 720

ccuucccagc agcagaaucu guugaguugc ugccacaaac aaaaaauaca auaaauauuu 780

gaacccccuc ccccccagca caaccccccc aaaacaaccc aacccacgag gaccaucggg 840

ggcagagucg uuggagacug aagaggaaga ggaggaggag aaggggagug agcggccgcc 900

cccagggcgg agauccagga gcuggcggcc gccgauccga uggagaaggg gggacccagg 960

ccagcaggag acaggacccc cgaagcugag gccuugggau ggagcagaag ccggaguggc 1020

ggggcacgcu gccgccuucc ccaucacgga ggguccagac uguccacucg gggguggagu 1080

gagacugacu gcaagcccca cccuccuuga gacuggagcu ggcgucugca uacgagagac 1140

uugguugaac uugguugguc cuugucugca cccucgacaa gaccacacuu ugggacuugg 1200

gagcuggggc ugaaguugcu cuguacccau gaacucccag uuugcgaauu auagagacaa 1260

ucuauuuugu uacuugcacu uguuauucga accacugaga gcgagauggg aagcauagau 1320

aucuauauuu uuauuucuac uaugagggcc uuguaauaaa uuucuaaagc cucugaaaaa 1380

aaaaaaaaaa aaa 1393

[0018]

<210> 10
<211> 160
<212> PRT
<213> 智人

<400> 10

Met Thr Leu Glu Glu Leu Val Ala Cys Asp Asn Ala Ala Gln Lys Met
1 5 10 15

Gln Thr Val Thr Ala Ala Val Glu Glu Leu Leu Val Ala Ala Gln Arg
20 25 30

Gln Asp Arg Leu Thr Val Gly Val Tyr Glu Ser Ala Lys Leu Met Asn
35 40 45

Val Asp Pro Asp Ser Val Val Leu Cys Leu Leu Ala Ile Asp Glu Glu
50 55 60

Glu Glu Asp Asp Ile Ala Leu Gln Ile His Phe Thr Leu Ile Gln Ser
65 70 75 80

Phe Cys Cys Asp Asn Asp Ile Asn Ile Val Arg Val Ser Gly Met Gln
85 90 95

Arg Leu Ala Gln Leu Leu Gly Glu Pro Ala Glu Thr Gln Gly Thr Thr
100 105 110

Glu Ala Arg Asp Leu His Cys Leu Leu Val Thr Asn Pro His Thr Asp
115 120 125

Ala Trp Lys Ser His Gly Leu Val Glu Val Ala Ser Tyr Cys Glu Glu
130 135 140

Ser Arg Gly Asn Asn Gln Trp Val Pro Tyr Ile Ser Leu Gln Glu Arg
145 150 155 160

<210> 11
<211> 4743
<212> RNA
<213> 智人

[0019]

<400> 11
cgcuucaugu ggcccggccc gcgacggccg gcggcuggga gcggcgaggc ggcggcggcg 60

gcgaguggcg gcccgcgagg cccgggaggc gguggccgag gcccaggcgg uggcggcggc 120

ggcccaggag gcggcggacg gggagcugcg ggagcaggcc cggccuggcu cucuagcggc 180

cgccuggcug cagcaugcgc gcccgccggg ggcugcugcg gcugccgcgc cgcucgcugc 240

ucgccgcgcu cuucuucuuu ucucucucgu ccucgcugcu guacuucguc uauguggcgc 300

ccggcauagu gaacaccuac cucuucauga ugcaagccca aggcauucug auccgggaca 360

acgugagaac aaucggugcu cagguuuaug agcaggugcu ucggagugcu uaugccaaga 420

ggaacagcag uguaaaugac ucagauuauc cucuugacuu gaaccacagu gaaaccuucc 480

ugcaaacuac aacauuucuu ccugaagacu ucaccuacuu ugcaaaccau accugcccug 540

aaagacuccc uuccaugaag ggcccaauag acauaaacau gagugaaauu ggaauggauu 600

acauucauga acucuucucc aaagacccaa ccaucaagcu cggaggucac uggaagccuu 660

cugauugcau gccucggugg aagguggcga uccuuauccc cuuccggaac cgccacgagc 720

accucccagu ccuguucaga caccugcuuc ccaugcucca gcgccagcgc uugcaguuug 780

cauuuuaugu gguugaacaa guugguaccc aacccuuuaa ucgagccaug cuuuucaacg 840

uuggcuuuca agaggcaaug aaagacuugg auugggacug uuugauuuuu caugauguag 900

aucacauacc ggaaagugau cgcaacuauu auggaugugg acagaugccg aggcauuuug 960

caaccaaauu ggauaaguau auguaucugc uuccuuauac cgaguucuuu ggcggaguga 1020

guggcuuaac aguggaacaa uuucggaaaa ucaauggcuu uccuaaugcu uucugggguu 1080

gggguggaga agaugacgac cucuggaaca gaguacagaa ugcaggcuau ucugugagcc 1140

ggccagaggg ugacacagga aaguacaagu ccauuccuca ucaccaucga ggagaagucc 1200

aguuucuugg aagguaugcu cugcugagga agucaaaaga acggcaaggg cuggauggcc 1260

ucaacaaccu gaacuacuuu gcaaacauca cauacgacgc cuuguauaaa aacauaacug 1320

[0020]

ucaaccugac acccgagcug gcucagguga acgaguacug agaggagaga auguacguuu 1380

gcuuuaccca ccgccaccaa gaaagcaguc cgaugagauu uuuuuuugga ggggggaggg 1440

ucuacacagc aagagaacag aaauacugug ucucaugaag gaucacagag uucagggggа 1500

aaaugugaca gcacacgcac aaacgccuuc acuggaucag ccgcuggaac ugagggagug 1560

agcuuggggа cuuccuucgu cagcacuggc uuucuguuuu cacaagacag acgucugucc 1620

cgcugcucuc uccccaucuc cuaccccaca uccugucuua gccgcagucu ccagaaccca 1680

ugaugaacug ugaucugccg ugguccugcc gugguccugc cguggagccu gucccuacac 1740

augaccuugg agccucuugg ccuucagagc agaggcaaac ccaccacagg gcagcugcgu 1800

uuuaggaaga gcaaaugaaa cuccacacca uucuucuaga ucucuggugu ucucuuuggu 1860

uucauuuuuu uaaaaaauua ccuucuuugg guggggauug aggguggagg ggagggуguu 1920

ugggaaagau aaauagacau aaauauauaa caaucacuuc uugaagaagu auaauuguaa 1980

auaagccaug uaaaaugccu uuuuaaaauu uaauuuucua gcuggcucca auucaaauug 2040

aggauuuaug uauuaggcca cuuacuuggu uggcaagugc aggaacucag uuaaaaugca 2100

guugaagaau gucaucuccc gaauugcugu cacuuuggcg agggagugga uauagggcau 2160

gucacaaaag aacaaaauaa cccgaccuuu auugcuggga gcuggcuucu gucccuuucu 2220

ucccccccc acgagucuug cccuugacuu cugcucugga uucacucuuc ccugucggcc 2280

gcgcaugugc ucaucccacu cuccgcuaag cgggaggcug cuguuagagc aggcugcuuc 2340

cugccuaaag caggcccuuc ggggcucgcu gcacacacau cucuggcucu ccaggcuucg 2400

uguucugucu uuucaucagc auggcggggc gggggggcggg gggcgggggu guguauggga 2460

aucccucccc cucuuacuuu uucucuugug gaacuuggcc acaguuucug aacaaugugc 2520

cuacauuacc agcuggcuuc agugauuccu cuguguccu uuuugguuuc uggaaagauu 2580

cuuugucaac auuaguaacu gauacauaga accaaggagc acucaaauag ggagccagga 2640

[0021]

gccagggagc uggugacacu ugugugcugu ggggcagcug ggauccaggu aagaccggau 2700

ugaagcuuug aaauuagacu aacaaagcuc cagacagcaa gagcccaggu gcacugcuca 2760

caccccacc ugcauuuuga agucauauua uuuuuuguuu uguuuuuuaa gacggucugg 2820

cucugucgcc uaagcuggag ugugguggca cgaucacagc ucacugcagc cuccaucucc 2880

uaggcucaag ccauuuuccc accucagccu cccgaguagc ugggacuaca ggugcacacc 2940

accacaccug gcuaauuuuu uguauuuuua guagagacag ggguuucuuc cauguugccc 3000

aggcuggucu cgaacuccug gacucaagca auccgcccac cuugacuucc caaagugcug 3060

ggauuauggg cgggugugag ccauugcgcc cagccuugaa gucauguucu aaauuguauu 3120

ugaauuugug ccucuuuguu uuuccccaaa ccaaagcccu caaauuguag ucucugucgg 3180

cuucugcaga auucuggaaa augccaguuu uccucccccg cccuuguuuu ccauaaaaca 3240

uauuuauaua uugugaugag gaguacuuuc ugaagaguac uucguauuuu uuuuuaauug 3300

ccuuguuugc cuucaacuuc cuugauuuuc auaguuuaca ugggugugug uaggggugug 3360

uguguguaug uguguggguu agggcuuuuu ucguugcaug ugaugguucu guggacauau 3420

gaucccccaca aacuguggga gugauuggcc aggccuuguu uuguuuguuu guuuguuugu 3480

guuuuuguuc uuuugaagaa uagaguggua uuuagaaaau aaauugcauu gcaaagcucu 3540

uaucggcuca uaugagagag cagguuccug cccuugaaaa ugccgguaag cuauagcaua 3600

uguuuuuuaa gacuuaagca uuucaugcuu uaaaauaccu ucacaaguga acauuacaca 3660

cagaaguuca uuugguuuuc cuuuguuuua uggugcauau agcaauaaag acccccccucc 3720

acccugcaac ccccaucccc caccgggccu uuguccccugc cuuggcuuuu cuccccuucu 3780

cauucuccuc uccccuuucc ucacugaagg cugugaguug cuuucaaugu gacaacacua 3840

ugaugucauu uggaaggauu ugccaggaca gacugauucu gaguccuggg ugccguaugu 3900

guaugcggca guguugucag gcgaucuugu uugaagcucu auguugccau aauuaccauc 3960

[0022]

aaguacacac uguuggcaaa aggcuaacac cugacuuuag aaaaugcuga uuugagaaca 4020

aaaggaaagg ucuuuuuuca cugcuuaaag uggggucacu uugauaccuu ugcggucaug 4080

ucugugucug augaguguag aaucucugga ugugcacugu cagucaugug uccaccaggc 4140

cucgaauauc auaugggaaa ugucauaguu aaaaacguac agccaggccc gugugcuguu 4200

aauaguguga aauugucaug uuaaaaaaaaa aaacaggaac caaaugugac cuugugcaua 4260

uauugguagc ugaaaaucuu caaggcuacu gauggguggc cccuuaaucu ugucuuugau 4320

ugcugugugc agggaaaggu gucccguuu guucaugcug uuuuggggggg ugggggggua 4380

uuugcaagaa uacucauuuu gacauaauag guccucuugu cagagauccu cuaccacaga 4440

cauuaauagc ugagcaggag ccacauggau ugauuguauc cacucaccau ugacgauggc 4500

auugagcgua gcuagcuuau uuccaucacu acguguuuuu gagcuugcuc uuacguuuua 4560

agaggugcca gggguacauu uuugcacuga aaucuaaaga uguuuuaaaa aacacuuuuc 4620

acaaaaauag uccuuuguca uuacauuauu uacucaugug uuuguacauu uuuguauguu 4680

aauuuaugaa ugauuuuuuc aguaaaaaau acauauucaa gaaccaaaaa aaaaaaaaaa 4740

aaa 4743

<210> 12
<211> 388
<212> PRT
<213> 智人

<400> 12

Met Arg Ala Arg Arg Gly Leu Leu Arg Leu Pro Arg Arg Ser Leu Leu
1 5 10 15

Ala Ala Leu Phe Phe Phe Ser Leu Ser Ser Ser Leu Leu Tyr Phe Val
20 25 30

Tyr Val Ala Pro Gly Ile Val Asn Thr Tyr Leu Phe Met Met Gln Ala
35 40 45

[0023]

Gln Gly Ile Leu Ile Arg Asp Asn Val Arg Thr Ile Gly Ala Gln Val
50 55 60

Tyr Glu Gln Val Leu Arg Ser Ala Tyr Ala Lys Arg Asn Ser Ser Val
65 70 75 80

Asn Asp Ser Asp Tyr Pro Leu Asp Leu Asn His Ser Glu Thr Phe Leu
85 90 95

Gln Thr Thr Thr Phe Leu Pro Glu Asp Phe Thr Tyr Phe Ala Asn His
100 105 110

Thr Cys Pro Glu Arg Leu Pro Ser Met Lys Gly Pro Ile Asp Ile Asn
115 120 125

Met Ser Glu Ile Gly Met Asp Tyr Ile His Glu Leu Phe Ser Lys Asp
130 135 140

Pro Thr Ile Lys Leu Gly Gly His Trp Lys Pro Ser Asp Cys Met Pro
145 150 155 160

Arg Trp Lys Val Ala Ile Leu Ile Pro Phe Arg Asn Arg His Glu His

165 170 175

Leu Pro Val Leu Phe Arg His Leu Leu Pro Met Leu Gln Arg Gln Arg
180 185 190

Leu Gln Phe Ala Phe Tyr Val Val Glu Gln Val Gly Thr Gln Pro Phe
195 200 205

Asn Arg Ala Met Leu Phe Asn Val Gly Phe Gln Glu Ala Met Lys Asp
210 215 220

Leu Asp Trp Asp Cys Leu Ile Phe His Asp Val Asp His Ile Pro Glu
225 230 235 240

Ser Asp Arg Asn Tyr Tyr Gly Cys Gly Gln Met Pro Arg His Phe Ala
245 250 255

Thr Lys Leu Asp Lys Tyr Met Tyr Leu Leu Pro Tyr Thr Glu Phe Phe
260 265 270

Gly Gly Val Ser Gly Leu Thr Val Glu Gln Phe Arg Lys Ile Asn Gly
[0024] 275 280 285

Phe Pro Asn Ala Phe Trp Gly Trp Gly Gly Glu Asp Asp Asp Leu Trp
290 295 300

Asn Arg Val Gln Asn Ala Gly Tyr Ser Val Ser Arg Pro Glu Gly Asp
305 310 315 320

Thr Gly Lys Tyr Lys Ser Ile Pro His His His Arg Gly Glu Val Gln
325 330 335

Phe Leu Gly Arg Tyr Ala Leu Leu Arg Lys Ser Lys Glu Arg Gln Gly
340 345 350

Leu Asp Gly Leu Asn Asn Leu Asn Tyr Phe Ala Asn Ile Thr Tyr Asp
355 360 365

Ala Leu Tyr Lys Asn Ile Thr Val Asn Leu Thr Pro Glu Leu Ala Gln
370 375 380

Val Asn Glu Tyr
385

<210> 13
<211> 1664
<212> RNA
<213> 智人

<400> 13

[0025]

ucucugcaau ccgggggcua aagcaaaagc gaaagcgaau acuccuuagc agcggucugg 60

uccuggagcu gagcucgcca ccucccaggg accccagccu ugcgucccgu ugggucacug 120

cuggggacaa uuggccaugg ccucgccgca gcuccggggc uauggagucc aggccauucc 180

uguguugcug cugcugcugu ugcuacuguu gcucccgcug agggugacgc cgggcaccac 240

guguccaccu cccguaucua uugagcaugc ugacauccgg gucaagaauu acagugugaa 300

cuccagggag agguaugucu guaacucugg cuuuaagcgg aaagcuggaa cauccacccu 360

gauugagugu gugaucaaca agaacacaaa uguugcccac uggacaacuc ccagccucaa 420

gugcaucaga gaccccuccc uagcucacua caguccagug ccaacaguag ugacaccaaa 480

ggugaccuca cagccagaga gccccucccc cucugcaaaa gagccagaag cuuucucucc 540

caaaucagau accgcaauga ccacagagac agcuauuaug ccuggcucca ggcugacacc 600

aucccaaaca acuucugcag gaacuacagg gacaggcagu cacaaguccu cccgagcccc 660

aucucuugca gcaacaauga ccuuggagcc uacagccucc accucccuca ggauaacaga 720

gauuucuccc cacaguucca aaaugacgaa aguggccauc ucuacaucgg uccucuuggu 780

uggugcaggg guugugaugg cuuuccuggc cugguacauc aaaucaaggc agccuucuca 840

gccgugccgu guugaggugg aaaccaugga aacaguacca augacuguga gggccagcag 900

caaggaggau gaagacacag gagccuaacc acacgauuuc agaaacucag ggagaccugc 960

ccagcugauc cugaagagaa gauacaaggg caguuagucc agcugcgccu ggacacagga 1020

gaaagcccaa ugugauaaua gaggucucug guaugaucug uuuuacugag ccugggugcc 1080

ucccauauuc aggccuggau ccccggaguc cggaaggaca ccaccuuucu uccugguuca 1140

ucacagaggc caacuuccca gaguacaagc agccugagcu cuccugggag ucuccauuaa 1200

aagccucgag uuccacucag agauuaacuc aaagcagcug aucugcuaga cucuuuuucu 1260

auucccuacu cugacuugca guuuacagag auugacaagg cucccauugu cuuccaaggc 1320

uccucuggca caggagaugu cuguaaagaa gacagcaaca uuugagcucc ugaagacuug 1380

gcccuuugcu gcuuugcacc uauuggagga gagcagagaa cagaagaaga gauacugagc 1440

caaugaaccc uuucguauag gauucaugac aaaaccaaac ucagugacua uauauguaug 1500

ugugugugug uguguaugua aaaguguaua uuuacauaua cauuuauauu uauacuuucu 1560

uuucuauuau aucuacauau uguauaugau uuauauuuga aagugcuuug uguagacaaa 1620

auaaaauauc uauuuucagu acaaaaagca uuaaaauuau caac 1664

<210> 14
<211> 267
<212> PRT
<213> 智人

[0026]

<400> 14

Met Ala Pro Arg Arg Ala Arg Gly Cys Arg Thr Leu Gly Leu Pro Ala
1 5 10 15

Leu Leu Leu Leu Leu Leu Leu Arg Pro Pro Ala Thr Arg Gly Ile Thr
20 25 30

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
35 40 45

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
50 55 60

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
65 70 75 80

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
85 90 95

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr

100 105 110

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
115 120 125

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
130 135 140

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
145 150 155 160

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
165 170 175

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
180 185 190

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
195 200 205

Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
210 215 220

[0027]

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
225 230 235 240

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
245 250 255

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu
260 265

<210> 15
<211> 4753
<212> RNA
<213> 智人

<400> 15
cuuuggaaag ucccguggaa aucccgggc cuacaacccg cauacaacug aaacggggca 60

aagcagacug cgcagucugc agucuucgug gcgggccaag cgagcuugga gcccgcgggg 120

gcggagcggu gagagcggcc gccaagagag aucacacccc cagccgaccc ugccagcgag 180

cgagcccgac cccaggcguc cauggagcgu cgccuccgcc cggucccugc cccgaccccc 240

gccugcggcg cgcuccugcc uugaccagga cuugggacuu ugcgaaagga ucgcggggcc 300

cggagaggua accgccgcgc cucccggaga gguaaccgcc gcgccucccg gagagguguu 360

ggagagcaca auggcugaac aaguccuucc ucaggcuuug uauuugagca auaugcggaa 420

agcugugaag auacgggaga gaacuccaga agacauuuuu aaaccuacua augggaucau 480

ucaucauuuu aaaaccaugc accgauacac acuggaaaug uucagaacuu gccaguuuug 540

uccucaguuu cgggagauca uccacaaagc ccucaucgac agaaacaucc aggccacccu 600

ggaaagccag aagaaacuca acuggugucg agaaguccgg aagcuugugg cgcugaaaac 660

gaacggugac ggcaauugcc ucaugcaugc cacuucucag uacauguggg gcguucagga 720

cacagacuug guacugagga aggcgcuguu cagcacgcuc aaggaaacag acacacgcaa 780

cuuuaaauuc cgcuggcaac uggagucucu caaaucucag gaauuuguug aaacggggcu 840

[0028]

uugcuaugau acucggaacu ggaaugauga augggacaau cuuaucaaaa uggcuuccac 900

agacacaccc auggcccgaa guggacuuca guacaacuca cuggaagaaa uacacauauu 960

uguccuuugc aacauccuca gaaggccaau cauugucauu ucagacaaaa ugcuaagaag 1020

uuuggaauca gguuccaauu ucgccccuuu gaaaagugggu ggaauuuacu ugccucucca 1080

cuggccugcc caggaaugcu acagauaccc cauuguucuc ggcuaugaca gccaucauuu 1140

uguacccuug gugacccuga aggacagugg gccugaaauc cgagcuguuc cacuuguuaa 1200

cagagaccgg ggaagauuug aagacuuaaa aguucacuuu uugacagauc cugaaaauga 1260

gaugaaggag aagcucuuaa aagaguacuu aauggugaua gaaaucccg uccaaggcug 1320

ggaccauggc acaacucauc ucaucaaugc cgcaaaguug gaugaagcua acuuaccaaa 1380

agaaaucaau cugguagaug auuacuuuga acuuguucag caugaguaca agaaauggca 1440

ggaaaacagc gagcagggga ggagagaggg gcacgcccag aaucccaugg aaccuuccgu 1500

gccccagcuu ucucucaugg auguaaaaug ugaaacgccc aacugccccu ucuucauguc 1560

ugugaacacc cagccuuuau gccaugagug cucagagagg cggcaaaaga aucaaaacaa 1620

acucccaaag cugaacucca agccgggccc ugaggggcuc ccuggcaugg cgcucggggc 1680

cucucgggga gaagccuaug agcccuuggc guggaacccu gaggagucca cuggggggcc 1740

ucauucggcc ccaccgacag cacccagccc uuuucuguuc agugagacca cugccaugaa 1800

gugcaggagc cccggcugcc ccuucacacu gaaugugcag cacaacggau uuugugaacg 1860

uugccacaac gcccggcaac uucacgccag ccacgcccca gaccacacaa ggcacuugga 1920

ucccgggaag ugccaagccu gccuccagga uguuaccagg acauuuaaug ggaucugcag 1980

uacuugcuuc aaaaggacua cagcagaggc cuccuccagc cucagcacca gccucccucc 2040

uuccugucac cagcguucca agucagaucc cucgcggcuc guccggagcc ccucccccgca 2100

uucuugccac agagcuggaa acgacgcccc ugcuggcugc cugucucaag cugcacggac 2160

[0029]

uccuggggac aggacgggga cgagcaagug cagaaaagcc ggcugcgugu auuuugggac 2220

uccagaaaac aagggcuuuu gcacacugug uuucaucgag uacagagaaa acaaacauuu 2280

ugcugcugcc ucagggaaag ucagucccac agcguccagg uuccagaaca ccauuccgug 2340

ccuggggagg gaaugcggca cccuuggaag caccauguuu gaaggauacu gccagaagug 2400

uuucauugaa gcucagaauc agagauuuca ugaggccaaa aggacagaag agcaacugag 2460

aucgagccag cgcagagaug ugccucgaac cacacaaagc accucaaggc ccaagugcgc 2520

ccgggccucc ugcaagaaca uccuggccug ccgcagcgag gagcucugca uggaguguca 2580

gcaucccaac cagaggaugg gcccuggggc ccaccggggu gagccugccc ccgaagaccc 2640

ccccaagcag cguugccggg cccccgccug ugaucauuuu ggcaaugcca agugcaacgg 2700

cuacugcaac gaaugcuuuc aguucaagca gauguauggc uaaccggaaa caggugggguc 2760

accuccugca agaaguggggg ccucgagcug ucagucauca uggugcuauc cucugaaccc 2820

cucagcugcc acugcaacag ugggcuuaag ggugucugag caggagagga aagauaagcu 2880

cuucguggug cccacgaugc ucagguuugg uaacccggga guguucccag guggccuuag 2940

aaagcaaagc uuguaacugg caagggauga ugucagauuc agcccaaggu uccuccucuc 3000

cuaccaagca ggaggccagg aacuucuuug gacuuggaag gugugcgggg acuggccgag 3060

gccccugcac ccugcgcauc aggacugcuu caucgucuug gcugagaaag ggaaaagaca 3120

cacaagucgc guggguugga gaagccagag ccauuccacc uccccucccc cagcaucucu 3180

cagagaugug aagccagauc cucauggcag cgaggcccuc ugcaagaagc ucaaggaagc 3240

ucagggaaaa uggacguauu cagagagugu uuguaguuca ugguuuuucc cuaccugccc 3300

gguuccuuuc cugaggaccc ggcagaaaug cagaaccauc cauggacugu gauucugagg 3360

cugcugagac ugaacauguu cacauugaca gaaaaacaag cugcucuuua uaauaugcac 3420

cuuuuaaaaa auuagaauau uuuacuggga agacguguaa cucuuugggu uauuacuguc 3480

[0030]

uuuacuucua aagaaguuag cuugaacuga ggaguaaaag uguguacaua uauaauauac 3540

ccuuacauua uguaugaggg auuuuuuuua auuauauuga aaugcugccc uagaaguaca 3600

auaggaaggc uaaauaauaa uaaccuguuu ucugguuguu guuggggcau gagcuugugu 3660

auacacugcu ugcauaaacu caaccagcug ccuuuuuaaa gggagcucua guccuuuuug 3720

uguaauucac uuuauuuauu uuauuacaaa cuucaagauu auuuaaguga agauauuucu 3780

ucagcucugg ggaaaaugcc acaguguucu ccugagagaa cauccuugcu uugagucagg 3840

cugugggcaa guuccugacc acagggagua aauuggccuc uuugauacac uuuugcuugc 3900

cuccccagga aagaaggaau ugcauccaag guauacauac auauucaucg auguuucgug 3960

cuucuccuua ugaaacucca gcuauguaau aaaaaacuau acucuguguu cuguuaaugc 4020

cucugagugu ccuaccuccu uggagaugag auagggaagg agcagggaug agacuggcaa 4080

uggucacagg gaaagaugug gccuuuugug augguuuuau uuucuguuaa cacugugucc 4140

uggggggcu gggaaguccc cugcauccca ugguacccug guauugggac agcaaaagcc 4200

aguaaccaug aguaugagga aaucucuuuc uguugcuggc uuacaguuuc ucugugugcu 4260

uuguggguugc ugucauauuu gcucuagaag aaaaaaaaaa aaggagggga aaugcauuuu 4320

ccccagagau aaaggcugcc auuuuggggg ucuguacuua uggccugaaa auauuuguga 4380

uccauaacuc uacacagccu uuacucauac uauuaggcac acuuuccccu uagagccccc 4440

uaaguuuuuc ccagacgaau cuuuauaauu ucuuuccaaa gauaccaaau aaacuucagu 4500

guuuucaucu aauucucuua aaguugauau cuuaauauuu uguguugauc auuauuucca 4560

uucuuaaugu gaaaaaaagu aauuauuuau acuuauuaua aaaaguauuu gaaauuugca 4620

cauuuaauug ucccuaauag aaagccaccu auucuuuguu ggauuucuuc aaguuuuucu 4680

aaauaaaugu aacuuuucac aagagucaac auuaaaaaau aaauuauuua agaacagaaa 4740

aaaaaaaaaa aaa 4753

[0031]

<210> 16
<211> 790
<212> PRT
<213> 智人

<400> 16

Met Ala Glu Gln Val Leu Pro Gln Ala Leu Tyr Leu Ser Asn Met Arg
1 5 10 15

Lys Ala Val Lys Ile Arg Glu Arg Thr Pro Glu Asp Ile Phe Lys Pro
20 25 30

Thr Asn Gly Ile Ile His His Phe Lys Thr Met His Arg Tyr Thr Leu
35 40 45

Glu Met Phe Arg Thr Cys Gln Phe Cys Pro Gln Phe Arg Glu Ile Ile
50 55 60

His Lys Ala Leu Ile Asp Arg Asn Ile Gln Ala Thr Leu Glu Ser Gln
65 70 75 80

Lys Lys Leu Asn Trp Cys Arg Glu Val Arg Lys Leu Val Ala Leu Lys
85 90 95

Thr Asn Gly Asp Gly Asn Cys Leu Met His Ala Thr Ser Gln Tyr Met
100 105 110

Trp Gly Val Gln Asp Thr Asp Leu Val Leu Arg Lys Ala Leu Phe Ser
115 120 125

Thr Leu Lys Glu Thr Asp Thr Arg Asn Phe Lys Phe Arg Trp Gln Leu
130 135 140

Glu Ser Leu Lys Ser Gln Glu Phe Val Glu Thr Gly Leu Cys Tyr Asp
145 150 155 160

Thr Arg Asn Trp Asn Asp Glu Trp Asp Asn Leu Ile Lys Met Ala Ser
165 170 175

Thr Asp Thr Pro Met Ala Arg Ser Gly Leu Gln Tyr Asn Ser Leu Glu
180 185 190

[0032] Glu Ile His Ile Phe Val Leu Cys Asn Ile Leu Arg Arg Pro Ile Ile
195 200 205

Val Ile Ser Asp Lys Met Leu Arg Ser Leu Glu Ser Gly Ser Asn Phe
210 215 220

Ala Pro Leu Lys Val Gly Gly Ile Tyr Leu Pro Leu His Trp Pro Ala
225 230 235 240

Gln Glu Cys Tyr Arg Tyr Pro Ile Val Leu Gly Tyr Asp Ser His His
245 250 255

Phe Val Pro Leu Val Thr Leu Lys Asp Ser Gly Pro Glu Ile Arg Ala
260 265 270

Val Pro Leu Val Asn Arg Asp Arg Gly Arg Phe Glu Asp Leu Lys Val
275 280 285

His Phe Leu Thr Asp Pro Glu Asn Glu Met Lys Glu Lys Leu Leu Lys
290 295 300

Glu Tyr Leu Met Val Ile Glu Ile Pro Val Gln Gly Trp Asp His Gly

305 310 315 320

Thr Thr His Leu Ile Asn Ala Ala Lys Leu Asp Glu Ala Asn Leu Pro
325 330 335

Lys Glu Ile Asn Leu Val Asp Asp Tyr Phe Glu Leu Val Gln His Glu
340 345 350

Tyr Lys Lys Trp Gln Glu Asn Ser Glu Gln Gly Arg Arg Glu Gly His
355 360 365

Ala Gln Asn Pro Met Glu Pro Ser Val Pro Gln Leu Ser Leu Met Asp
370 375 380

Val Lys Cys Glu Thr Pro Asn Cys Pro Phe Phe Met Ser Val Asn Thr
385 390 395 400

Gln Pro Leu Cys His Glu Cys Ser Glu Arg Arg Gln Lys Asn Gln Asn
405 410 415

Lys Leu Pro Lys Leu Asn Ser Lys Pro Gly Pro Glu Gly Leu Pro Gly
[0033] 420 425 430

Met Ala Leu Gly Ala Ser Arg Gly Glu Ala Tyr Glu Pro Leu Ala Trp
435 440 445

Asn Pro Glu Glu Ser Thr Gly Gly Pro His Ser Ala Pro Pro Thr Ala
450 455 460

Pro Ser Pro Phe Leu Phe Ser Glu Thr Thr Ala Met Lys Cys Arg Ser
465 470 475 480

Pro Gly Cys Pro Phe Thr Leu Asn Val Gln His Asn Gly Phe Cys Glu
485 490 495

Arg Cys His Asn Ala Arg Gln Leu His Ala Ser His Ala Pro Asp His
500 505 510

Thr Arg His Leu Asp Pro Gly Lys Cys Gln Ala Cys Leu Gln Asp Val
515 520 525

Thr Arg Thr Phe Asn Gly Ile Cys Ser Thr Cys Phe Lys Arg Thr Thr
530 535 540

Ala Glu Ala Ser Ser Ser Leu Ser Thr Ser Leu Pro Pro Ser Cys His
545 550 555 560

Gln Arg Ser Lys Ser Asp Pro Ser Arg Leu Val Arg Ser Pro Ser Pro
565 570 575

His Ser Cys His Arg Ala Gly Asn Asp Ala Pro Ala Gly Cys Leu Ser
580 585 590

Gln Ala Ala Arg Thr Pro Gly Asp Arg Thr Gly Thr Ser Lys Cys Arg
595 600 605

Lys Ala Gly Cys Val Tyr Phe Gly Thr Pro Glu Asn Lys Gly Phe Cys
610 615 620

Thr Leu Cys Phe Ile Glu Tyr Arg Glu Asn Lys His Phe Ala Ala Ala
625 630 635 640

Ser Gly Lys Val Ser Pro Thr Ala Ser Arg Phe Gln Asn Thr Ile Pro
645 650 655

[0034] Cys Leu Gly Arg Glu Cys Gly Thr Leu Gly Ser Thr Met Phe Glu Gly
660 665 670

Tyr Cys Gln Lys Cys Phe Ile Glu Ala Gln Asn Gln Arg Phe His Glu
675 680 685

Ala Lys Arg Thr Glu Glu Gln Leu Arg Ser Ser Gln Arg Arg Asp Val
690 695 700

Pro Arg Thr Thr Gln Ser Thr Ser Arg Pro Lys Cys Ala Arg Ala Ser
705 710 715 720

Cys Lys Asn Ile Leu Ala Cys Arg Ser Glu Glu Leu Cys Met Glu Cys
725 730 735

Gln His Pro Asn Gln Arg Met Gly Pro Gly Ala His Arg Gly Glu Pro
740 745 750

Ala Pro Glu Asp Pro Pro Lys Gln Arg Cys Arg Ala Pro Ala Cys Asp
755 760 765

His Phe Gly Asn Ala Lys Cys Asn Gly Tyr Cys Asn Glu Cys Phe Gln
770 775 780

Phe Lys Gln Met Tyr Gly
785 790

<210> 17
<211> 1216
<212> RNA
<213> 智人

<400> 17

[0035]

ggcagcugca cggcuccugg ccccggagca ugcgcgagag ccgccccgga gcgccccgga 60

gccccccgcc gucccgcccg cggcgucccg cgccccgccg ccagcgcacc cccggacgcu 120

auggcccacc ccuccggcug gccccuucug uaggauggua gcacacaacc agguggcagc 180

cgacaaugca gucuccacag cagcagagcc ccgacggcgg ccagaaccuu ccuccucuuc 240

cuccuccucg cccgcggccc ccgcgcgccc gcggccgugc cccgcggucc cggccccggc 300

ccccggcgac acgcacuucc gcacauuccg uucgcacgcc gauuaccggc gcaucacgcg 360

cgccagcgcg cuccuggacg ccugcggauu cuacuggggg ccccugagcg ugcacggggc 420

gcacgagcgg cugcgcgccg agcccguggg caccuuccug gugcgcgaca gccgccagcg 480

gaacugcuuu uucgcccuua gcgugaagau ggccucggga cccacgagca uccgcgugca 540

cuuucaggcc ggccgcuuuc accuggaugg cagccgcgag agcuucgacu gccucuucga 600

gcugcuggag cacuacgugg cggcgccgcg ccgcaugcug ggggccccgc ugcgccagcg 660

ccgcgugcgg ccgcugcagg agcugugccg ccagcgcauc guggccaccg ugggccgcga 720

gaaccuggcu cgcaucccccc ucaaccccgu ccuccgcgac uaccugagcu ccuuccccuu 780

ccagauuuga ccggcagcgc ccgccgugca cgcagcauua acugggaugc cguguuauuu 840

uguuauuacu ugccuggaac cauguggggua cccucccccgg ccuggguugg agggagcgga 900

uggguguagg ggcgaggcgc cucccgcccu cggcuggaga cgaggccgca gaccccuucu 960

caccucuuga ggggguccuc ccccuccugg ugcucccucu gggucccccu gguuguugua 1020

gcagcuuaac uguaucugga gccaggaccu gaacucgcac cuccuaccuc uucauguuua 1080

cauauaccca guaucuuugc acaaaccagg gguuggggga gggucucugg cuuuauuuuu 1140

cugcugugca gaauccuauu uuauauuuuu uaaagucagu uuagguaaua aacuuuauua 1200

ugaaaguuuu uuuuuu 1216

<210> 18
<211> 211
<212> PRT
<213> 智人

<400> 18

Met Val Ala His Asn Gln Val Ala Ala Asp Asn Ala Val Ser Thr Ala
1 5 10 15

Ala Glu Pro Arg Arg Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser Ser
20 25 30

[0036]

Pro Ala Ala Pro Ala Arg Pro Arg Pro Cys Pro Ala Val Pro Ala Pro
35 40 45

Ala Pro Gly Asp Thr His Phe Arg Thr Phe Arg Ser His Ala Asp Tyr
50 55 60

Arg Arg Ile Thr Arg Ala Ser Ala Leu Leu Asp Ala Cys Gly Phe Tyr
65 70 75 80

Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu Arg Ala Glu
85 90 95

Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys Phe
100 105 110

Phe Ala Leu Ser Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg Val
115 120 125

His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg Glu Ser Phe
130 135 140

Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg Arg
145 150 155 160

Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln Glu
165 170 175

Leu Cys Arg Gln Arg Ile Val Ala Thr Val Gly Arg Glu Asn Leu Ala
180 185 190

Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe Pro
195 200 205

Phe Gln Ile
210

<210> 19
<211> 1794
<212> RNA
<213> 智人

<400> 19

[0037]

auuucuuuau aaaccacaac ucugggcccg caauggcagu ccacugccuu gcugcaguca 60

cagaauggaa aucugcagag gccuccgcag ucaccuaauc acucuccucc ucuuccuguu 120

ccauucagag acgaucugcc gacccucugg gagaaaaucc agcaagaugc aagccuucag 180

aaucugggau guuaaccaga agaccuucua ucugaggaac aaccaacuag uugcuggaua 240

cuugcaagga ccaaauguca auuuagaaga aaagauagau gugguaccca uugagccuca 300

ugcucuguuc uugggaaucc auggagggaa gaugugccug uccuguguca agucugguga 360

ugagaccaga cuccagcugg aggcaguuaa caucacugac cugagcgaga acagaaagca 420

ggacaagcgc uucgccuuca uccgcucaga caguggcccc accaccaguu uugagucugc 480

cgccugcccc gguugguucc ucugcacagc gauggaagcu gaccagcccg ucagccucac 540

caauaugccu gacgaaggcg ucauggucac caaauucuac uuccaggagg acgaguagua 600

cugcccaggc cugccuguuc ccauucuugc auggcaagga cugcagggac ugccaguccc 660

ccugccccag ggcucccggc uaugggggca cugaggacca gccauugagg gguggacccu 720

cagaaggcgu cacaacaacc uggucacagg acucugccuc cucuucaacu gaccagccuc 780

caugcugccu ccagaauggu cuuucuaaug ugugaaucag agcacagcag ccccugcaca 840

aagcccuucc augucgccuc ugcauucagg aucaaacccc gaccaccugc ccaaccugcu 900

cuccucuugc cacugccucu uccucccuca uuccaccuuc ccaugcccug gauccaucag 960

gccacuugau gacccccaac caaguggcuc ccacacccug uuuuacaaaa aagaaaagac 1020

caguccauga gggagguuuu uaaggguuug uggaaaauga aaauuaggau uucaugauuu 1080

uuuuuuuuca gucccguga aggagagccc uucauuugga gauuauguuc uuucggggag 1140

aggcugagga cuuaaaauau uccugcauuu gugaaaugau ggugaaagua agugguagcu 1200

uuucccuucu uuuucuucuu uuuuugugau gucccaacuu guaaaaauua aaaguuaugg 1260

uacuauguua gccccauaau uuuuuuuuuc cuuuuaaaac acuuccauaa ucuggacucc 1320

ucuguccagg cacugcugcc cagccuccaa gcuccaucuc cacuccagau uuuuuacagc 1380

ugccugcagu acuuuaccuc cuaucagaag uuucucagcu cccaaggcuc ugagcaaaug 1440

[0038]

uggcuccugg ggguucuuuc uuccucugcu gaaggaauaa auugcuccuu gacauuguag 1500

agcuucuggc acuuggagac uuguaugaaa gauggcugug ccucugccug ucucccccac 1560

cgggcuggga gcucugcaga gcaggaaaca ugacucguau augucucagg ucccugcagg 1620

gccaagcacc uagccucgcu cuuggcaggu acucagcgaa ugaaugcugu auauguuggg 1680

ugcaaaguuc ccuacuuccu gugacuucag cucuguuuua caauaaaauc uugaaaaugc 1740

cuaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa 1794

<210> 20
<211> 177
<212> PRT
<213> 智人

<400> 20

Met Glu Ile Cys Arg Gly Leu Arg Ser His Leu Ile Thr Leu Leu Leu
1 5 10 15

Phe Leu Phe His Ser Glu Thr Ile Cys Arg Pro Ser Gly Arg Lys Ser
20 25 30

Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe
35 40 45

Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
50 55 60

Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
65 70 75 80

Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys
85 90 95

Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp
100 105 110

Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
115 120 125

[0039]

Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp
130 135 140

Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
145 150 155 160

Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp
165 170 175

Glu

<210> 21
<211> 4553
<212> RNA
<213> 智人

<400> 21
acgcgucugc ggccagcccg gacucuuuaa aagccggcgg ugcgcggggc aucccagcca 60

agccggagag gaggcgagca gcagggccug guggcgagag cgcggcuguc acugcgcccg 120

agcaucccag agcuuuccga gcggacgagc cggccgugcc gggcaucccc agccucgcua 180

cccucgcagc acacgucgag ccccgcacag gcgagggucc ggaacuuagc ccaaagcacg 240

uuuccccugg cagcgcagga aacgcccggc cgcgcgccgg cgcacgcccc ccucuccucc 300

uuuguuccgg gggucggcgg ccgcucuccu gccagcgucg ggaucucggc cccgggaggc 360

gggccgucgg gcgcagccgc gaagaugccg uuggaacuga cgcagagccg agugcagaag 420

aucugggugc ccguggacca caggcccucg uugcccagau ccuguggggcc aaagcugacc 480

aacuccccca ccgucaucgu caugguggggc cucccccgccc ggggcaagac cuacaucucc 540

aagaagcuga cucgcuaccu caacuggauu ggcgucccca caaaaguguu caacgucggg 600

gaguaucgcc gggaggcugu gaagcaguac agcuccuaca acuucuuccg ccccgacaau 660

gaggaagcca ugaaaguccg gaagcaaugu gccuuagcug ccuugagaga ugucaaaagc 720

uaccuggcga aagaaggggg acaaauugcg guuuucgaug ccaccaauac uacuagagag 780

[0040]

aggagacaca ugauccuuca uuuugccaaa gaaaaugacu uuaaggcguu uuucaucgag 840

ucggugugcg acgacccuac aguuguggcc uccaauauca uggaaguuaa aaucuccagc 900

ccggauuaca aagacugcaa cucggcagaa gccauggacg acuucaugaa gaggaucagu 960

ugcuaugaag ccagcuacca gccccucgac cccgacaaau gcgacaggga cuugucgcug 1020

aucaagguga uugacguggg ccggagguuc cuggugaacc gggugcagga ccacauccag 1080

agccgcaucg uguacuaccu gaugaacauc cacgugcagc cgcguaccau cuaccugugc 1140

cggcacggcg agaacgagca caaccuccag ggccgcaucg ggggcgacuc aggccugucc 1200

agccggggca agaaguuugc cagugcucug agcaaguucg uggaggagca gaaccugaag 1260

gaccugcgcg uguggaccag ccagcugaag agcaccaucc agacggccga ggcgcugcgg 1320

cugcccuacg agcaguggaa ggcgcucaau gagaucgacg cgggcgucug ugaggagcug 1380

accuacgagg agaucaggga caccuacccu gaggaguaug cgcugcggga gcaggacaag 1440

uacuauuacc gcuaccccac cggggagucc uaccaggacc ugguccagcg cuuggagcca 1500

gugaucaugg agcuggagcg gcaggagaau gugcugguca ucugccacca ggccguccug 1560

cgcugccugc uugccuacuu ccuggauaag agugcagagg agaugcccua ccugaaaugc 1620

ccucuucaca ccguccugaa acugacgccu gucgcuuaug gcugccgugu ggaauccauc 1680

uaccugaacg uggaguccgu cugcacacac cgggagaggu cagaggaugc aaagaaggga 1740

ccuaacccgc ucaugagacg caauaguguc accccgcuag ccagccccga acccaccaaa 1800

aagccucgca ucaacagcuu ugaggagcau guggccucca ccucggccgc ccugcccagc 1860

ugccugcccc cggaggugcc cacgcagcug ccuggacaaa acaugaaagg cucccggagc 1920

agcgcugacu ccuccaggaa acacugaggc agacgugucg guuccauucc auuuccauuu 1980

cugcagcuua gcuugugucc ugcccuccgc ccgaggcaaa acguauccug aggacuucuu 2040

ccggagaggg uggguggag cagcggggga gccuuggccg aagagaacca ugcuuggcac 2100

[0041]

cgucuguguc cccucggccg cuggacacca gaaagccacg uggguccccug gcgcccugcc 2160

uuuagccgug gggccccccac cuccacucuc uggguuuccu aggaaugucc agccucggag 2220

accuucacaa agccuuggga gggugaugag ugcugguccu gacaggaggc cgcuggggac 2280

acugugcugu uuuguuucgu uucugugauc ucccggcacg uuuggagcug ggaagaccac 2340

acugguggca gaauccuaaa auuaaaggag gcaggcuccu aguugcugaa aguuaaggaa 2400

uguguaaaac cuccacguga cuguuuggug caucuugacc ugggaagacg ccucauggga 2460

acgaacuugg acagguguug gguugaggcc ucuucugcag gaagucccug agcugagacg 2520

caaguuggcu gggugguccg cacccuggcu cuccugcagg uccacacacc uuccaggccu 2580

guggccugcc uccaaagaug ugcaagggca ggcuggcugc acggggagag ggaaguauuu 2640

ugccgaaaua ugagaacugg ggccuccugc ucccagggag cuccagggcc ccucucuccu 2700

cccaccugga cuuggggggа acugagaaac acuuuccugg agcugcuggc uuuugcacuu 2760

uuuugauggc agaaguguga ccugagaguc ccaccuucuc uucaggaacg uagauguugg 2820

ggugucuugc ccuggggggc uuggaaccuc ugaagguggg gagcggaaca ccuggcaucc 2880

uucccagca cuugcauuac cgucccugcu cuucccaggu ggggacagug gcccaagcaa 2940

ggccucacuc gcagccacuu cuucaagagc ugccugcaca cugucuugga gcaucugccu 3000

ugugccuggc acucugccgg ugccuuggga aggucggaag aguggacuuu guccuggccu 3060

ucccuucaug gcgucuauga cacuuuugug gugauggaaa gcaugggacc ugucgucuca 3120

gccuguuggu uucuccucau ugccucaaac ccugggguag gugggacggg gggucucgug 3180

cccagaugaa accauuugga aacucggcag cagaguuugu ccaaaugacc cuuuucagga 3240

ugucucaaag cuugugccaa aggucacuuu ucuuuccugc cuucugcugu gagcccugag 3300

auccuccucc cagcucaagg gacagguccu gggugagggu gggagauuua gacaccugaa 3360

acugggcgug gagagaagag ccguugcugu uuguuuuuug ggaagagcuu uuaaagaaug 3420

[0042]

cauguuuuuu uccugguugg aauugaguag gaacugaggc ugugcuucag guaugguaca 3480

aucaaguggg ggauuuucau gcugaaccau ucaagcccuc cccgcccguu gcacccacuu 3540

uggcuggcgu cugcuggaga ggaugucucu guccgcauuc ccgugcagcu ccaggcucgc 3600

gcaguuuucu cucucucccu ggauguugag ucucaucaga auaugugggu agggggugga 3660

cgugcacggg ugcaugauug ugcuuaacuu gguuguauuu uucgauuuga cauggaaggc 3720

cuguugcuuu gcucuugaga auaguuucuc gugucccccu cgcaggccuc auucuuugaa 3780

caucgacucu gaaguuugau acagauaggg gcuugauagc uguggucccc ucucccccucu 3840

gacuaccuaa aaucaauacc uaaauacaga agccuugguc uaacacggga cuuuuaguuu 3900

gcgaagggcc uagauaggga gagagguaac augaaucugg acagggaggg agauacuaua 3960

gaaaggagaa cacugccuac uuugcaagcc agugaccugc cuuuugaggg gacauuggac 4020

gggggccggg ggcgggggguu ggguuugagc uacagucaug aacuuuuggc gucuacugau 4080

uccuccaacu cuccacccca caaaauaacg gggaccaaua uuuuuaacuu ugccuauuug 4140

uuuuugggug aguuuccccc cuccuuauuc uguccugaga ccacgggcaa agcucuucau 4200

uuugagagag aagaaaaacu guuuggaacc acaccaauga uauuuuucuu uguaauacuu 4260

gaaauuuauu uuuuuauuau uuugauagca gaugugcuau uuauuuauuu aauauguaua 4320

aggagccuaa acaauagaaa gcuguagaga uuggguuuca uuguuaauug guuugggagc 4380

cuccuaugug ugacuuauga cuucucugug uucuguguau uugucugaau uaaugaccug 4440

ggauauaaag cuaugcuagc uuucaaacag gagaugccuu ucagaaauuu guauauuuug 4500

caguugccag accaauaaaa uaccugguug aaauacaugg acgaaguaaa aaa 4553

<210> 22
<211> 520
<212> PRT
<213> 智人

[0043] <400> 22

Met Pro Leu Glu Leu Thr Gln Ser Arg Val Gln Lys Ile Trp Val Pro
1 5 10 15

Val Asp His Arg Pro Ser Leu Pro Arg Ser Cys Gly Pro Lys Leu Thr
20 25 30

Asn Ser Pro Thr Val Ile Val Met Val Gly Leu Pro Ala Arg Gly Lys
35 40 45

Thr Tyr Ile Ser Lys Lys Leu Thr Arg Tyr Leu Asn Trp Ile Gly Val
50 55 60

Pro Thr Lys Val Phe Asn Val Gly Glu Tyr Arg Arg Glu Ala Val Lys
65 70 75 80

Gln Tyr Ser Ser Tyr Asn Phe Phe Arg Pro Asp Asn Glu Glu Ala Met
85 90 95

Lys Val Arg Lys Gln Cys Ala Leu Ala Ala Leu Arg Asp Val Lys Ser
100 105 110

Tyr Leu Ala Lys Glu Gly Gly Gln Ile Ala Val Phe Asp Ala Thr Asn
115 120 125

Thr Thr Arg Glu Arg Arg His Met Ile Leu His Phe Ala Lys Glu Asn
130 135 140

Asp Phe Lys Ala Phe Phe Ile Glu Ser Val Cys Asp Asp Pro Thr Val
145 150 155 160

Val Ala Ser Asn Ile Met Glu Val Lys Ile Ser Ser Pro Asp Tyr Lys
165 170 175

Asp Cys Asn Ser Ala Glu Ala Met Asp Asp Phe Met Lys Arg Ile Ser
180 185 190

Cys Tyr Glu Ala Ser Tyr Gln Pro Leu Asp Pro Asp Lys Cys Asp Arg
195 200 205

Asp Leu Ser Leu Ile Lys Val Ile Asp Val Gly Arg Arg Phe Leu Val
210 215 220

[0044]

Asn Arg Val Gln Asp His Ile Gln Ser Arg Ile Val Tyr Tyr Leu Met
225 230 235 240

Asn Ile His Val Gln Pro Arg Thr Ile Tyr Leu Cys Arg His Gly Glu
245 250 255

Asn Glu His Asn Leu Gln Gly Arg Ile Gly Gly Asp Ser Gly Leu Ser
260 265 270

Ser Arg Gly Lys Lys Phe Ala Ser Ala Leu Ser Lys Phe Val Glu Glu
275 280 285

Gln Asn Leu Lys Asp Leu Arg Val Trp Thr Ser Gln Leu Lys Ser Thr
290 295 300

Ile Gln Thr Ala Glu Ala Leu Arg Leu Pro Tyr Glu Gln Trp Lys Ala
305 310 315 320

Leu Asn Glu Ile Asp Ala Gly Val Cys Glu Glu Leu Thr Tyr Glu Glu
325 330 335

Ile Arg Asp Thr Tyr Pro Glu Glu Tyr Ala Leu Arg Glu Gln Asp Lys
340 345 350

Tyr Tyr Tyr Arg Tyr Pro Thr Gly Glu Ser Tyr Gln Asp Leu Val Gln
355 360 365

Arg Leu Glu Pro Val Ile Met Glu Leu Glu Arg Gln Glu Asn Val Leu
370 375 380

Val Ile Cys His Gln Ala Val Leu Arg Cys Leu Leu Ala Tyr Phe Leu
385 390 395 400

Asp Lys Ser Ala Glu Glu Met Pro Tyr Leu Lys Cys Pro Leu His Thr
405 410 415

Val Leu Lys Leu Thr Pro Val Ala Tyr Gly Cys Arg Val Glu Ser Ile
420 425 430

Tyr Leu Asn Val Glu Ser Val Cys Thr His Arg Glu Arg Ser Glu Asp
435 440 445

Ala Lys Lys Gly Pro Asn Pro Leu Met Arg Arg Asn Ser Val Thr Pro
450 455 460

[0045]

Leu Ala Ser Pro Glu Pro Thr Lys Lys Pro Arg Ile Asn Ser Phe Glu
465 470 475 480

Glu His Val Ala Ser Thr Ser Ala Ala Leu Pro Ser Cys Leu Pro Pro
485 490 495

Glu Val Pro Thr Gln Leu Pro Gly Gln Asn Met Lys Gly Ser Arg Ser
500 505 510

Ser Ala Asp Ser Ser Arg Lys His
515 520

<210> 23
<211> 899
<212> RNA
<213> 智人

<400> 23
agccuacgca cgaaagugac uaggaggaag gauauuauaa agugaugcaa acagaaauuc 60

caccagccuc cauguaucau caugugucau aacucaguca agcucaguga gcauucucag 120

cacauugccu caacagcuuc aaggugagcc agcucaagac uuugcucucc accaggcaga 180

agaugacaga cugugaauuu ggauauauuu acaggcuggc ucaggacuau cugcagugcg 240

uccuacagau accacaaccu ggaucagguc caagcaaaac guccagagug cuacaaaaug 300

uugcguucuc aguccaaaaa gaaguggaaa agaaucugaa gucaugcuug gacaauguua 360

auguuguguc cguagacacu gccagaacac uauucaacca agugauggaa aaggaguuug 420

aagacggcau cauuaacugg ggaagaauug uaaccauauu ugcauuugaa gguauucuca 480

ucaagaaacu ucuacgacag caaauugccc cggaugugga uaccuauaag gagauuucau 540

auuuuguugc ggaguucaua augaauaaca caggagaaug gauaaggcaa aacggaggcu 600

gggaaaaugg cuuuguaaag aaguuugaac cuaaaucugg cuggaugacu uuucuagaag 660

uuacaggaaa gaucugugaa augcuaucuc uccugaagca auacuguuga ccagaaagga 720

cacuccauau ugugaaaccg gccuaauuuu ucugacugau auggaaacga uugccaacac 780

[0046]

auacuucuac uuuuaaauaa acaacuuuga ugauguaacu ugaccuucca gaguuaugga 840

aauuuugucc ccauguaaug aauaaauugu auguauuuuu cucuauaaaa aaaaaaaaa 899

<210> 24
<211> 175
<212> PRT
<213> 智人

<400> 24

Met Thr Asp Cys Glu Phe Gly Tyr Ile Tyr Arg Leu Ala Gln Asp Tyr
1 5 10 15

Leu Gln Cys Val Leu Gln Ile Pro Gln Pro Gly Ser Gly Pro Ser Lys
20 25 30

Thr Ser Arg Val Leu Gln Asn Val Ala Phe Ser Val Gln Lys Glu Val
35 40 45

Glu Lys Asn Leu Lys Ser Cys Leu Asp Asn Val Asn Val Val Ser Val
50 55 60

```
Asp Thr Ala Arg Thr Leu Phe Asn Gln Val Met Glu Lys Glu Phe Glu
65                  70                  75                  80

Asp Gly Ile Ile Asn Trp Gly Arg Ile Val Thr Ile Phe Ala Phe Glu
                85                  90                  95

Gly Ile Leu Ile Lys Lys Leu Leu Arg Gln Gln Ile Ala Pro Asp Val
            100                 105                 110

Asp Thr Tyr Lys Glu Ile Ser Tyr Phe Val Ala Glu Phe Ile Met Asn
        115                 120                 125

Asn Thr Gly Glu Trp Ile Arg Gln Asn Gly Gly Trp Glu Asn Gly Phe
    130                 135                 140

Val Lys Lys Phe Glu Pro Lys Ser Gly Trp Met Thr Phe Leu Glu Val
145                 150                 155                 160

Thr Gly Lys Ile Cys Glu Met Leu Ser Leu Leu Lys Gln Tyr Cys
                165                 170                 175
```

[0047]

<210> 25
<211> 1227
<212> RNA
<213> 智人

<400> 25

```
cuuugcagau aaauauggca cacuagcccc acguuuucug agacauuccu caauugcuua      60

gacauauucu gagccuacag cagaggaacc uccagucuca gcaccaugaa ucaaacugcc     120

auucugauuu gcugccuuau cuuucugacu cuaaguggca uucaaggagu accucucucu     180

agaacuguac gcuguaccug caucagcauu aguaaucaac cuguuaaucc aaggucuuua     240

gaaaaacuug aaauuauucc ugcaagccaa uuuuguccac guguugagau cauugcuaca     300

augaaaaaga agggugagaa gagaugucug aauccagaau cgaaggccau caagaauuua     360

cugaaagcag uuagcaagga aaggucuaaa agaucuccuu aaaaccagag gggagcaaaa     420

ucgaugcagu gcuuccaagg auggaccaca cagaggcugc cucucccauc acuucccuac     480
```

auggaguaua ugucaagcca uaauuguucu uaguuugcag uuacacuaaa aggugaccaa 540

ugauggucac caaaucagcu gcuacuacuc cuguaggaag guuaauguuc aucauccuaa 600

gcuauucagu aauaacucua cccuggcacu auaauguaag cucuacugag gugcuauguu 660

cuuaguggau guucugaccc ugcuucaaau auuuccccuca ccuuuccccau cuuccaaggg 720

uacuaaggaa ucuuucugcu uuggggguuua ucagaauucu cagaaucuca aauaacuaaa 780

agguaugcaa ucaaaucugc uuuuuaaaga augcucuuua cuucauggac uuccacugcc 840

auccucccaa ggggcccaaa uucuuucagu ggcuaccuac auacaauucc aaacacauac 900

aggaagguag aaauaucuga aaauguaugu guaaguauuc uuauuuaaug aaagacugua 960

caaaguagaa gucuuagaug uauauauuuc cuauauuguu uucaguguac auggaauaac 1020

auguaauuaa guacuaugua ucaaugagua acaggaaaau uuuaaaaaua cagauagaua 1080

uaugcucugc auguuacaua agauaaaugu gcugaauggu uuucaaaaua aaaaugaggu 1140

[0048]

acucuccugg aaauauuaag aaagacuauc uaaauguuga aagaucaaaa gguuaauaaa 1200

guaauuauaa cuaagaaaaa aaaaaaa 1227

<210> 26
<211> 98
<212> PRT
<213> 智人

<400> 26

Met Asn Gln Thr Ala Ile Leu Ile Cys Cys Leu Ile Phe Leu Thr Leu
1 5 10 15

Ser Gly Ile Gln Gly Val Pro Leu Ser Arg Thr Val Arg Cys Thr Cys
20 25 30

Ile Ser Ile Ser Asn Gln Pro Val Asn Pro Arg Ser Leu Glu Lys Leu
35 40 45

Glu Ile Ile Pro Ala Ser Gln Phe Cys Pro Arg Val Glu Ile Ile Ala
50 55 60

Thr Met Lys Lys Lys Gly Glu Lys Arg Cys Leu Asn Pro Glu Ser Lys
65 70 75 80

Ala Ile Lys Asn Leu Leu Lys Ala Val Ser Lys Glu Arg Ser Lys Arg
85 90 95

Ser Pro

<210> 27
<211> 1351
<212> RNA
<213> 智人

<400> 27

[0049]

gugauggaga gcaccagcaa agccuuaggg cccaucccug gccuccuguu acccacagag 60

ggguaggccc uuggcucucu uccacuauga cgucagcuuc cauucuuccu uucuuauaga 120

caauuuucca uuucaaggaa aucagagccc uuaauaguuc agugagguca cuuugcugag 180

cacaauccca uacccuucag ccucugcucc acagagccua agcaaaagau agaaacucac 240

aacuuccuug uuuuguuauc uggaaauuau cccaggaucu ggugcuuacu cagcauauuc 300

aaggaagguc uuacuucauu cuuccuugau ugugaccaug cccaggcucu cugcucccua 360

uaaaaggcag gcagagccac cgaggagcag agagguugag aacaacccag aaaccuucac 420

cucucaugcu gaagcucaca cccuugcccu ccaagaugaa gguuucugca gcgcuucugu 480

gccugcugcu cauggcagcc acuuucagcc cucagggacu ugcucagcca gauucaguuu 540

ccauuccaau caccugcugc uuuaacguga ucaauaggaa aauuccuauc cagaggcugg 600

agagcuacac aagaaucacc aacauccaau gucccaagga agcugugauc uucaagacca 660

aacggggcaa ggaggucugu gcugacccca aggagagaug ggucagggau uccaugaagc 720

aucuggacca aauauuucaa aaucugaagc caugagccuu cauacaugga cugagaguca 780

gagcuugaag aaaagcuuau uuauuuuccc caaccucccc caggugcagu gugacauuau 840

uuuauuauaa cauccacaaa gagauuauuu uuaaauaauu uaaagcauaa uauuucuuaa 900

aaaguauuua auuauauuua aguuguugau guuuuaacuc uaucugucau acauccuagu 960

gaauguaaaa ugcaaaaucc uggugaugug uuuuuuguuu uuguuuuccu gugagcucaa 1020

cuaaguucac ggcaaaaugu cauuguucuc ccuccuaccu gucuguagug uuuggggguc 1080

cucccaugga ucaucaaggu gaaacacuuu gguauucuuu ggcaaucagu gcuccuguaa 1140

gucaaaugug ugcuuuguac ugcuguuguu gaaauugaug uuacuguaua uaacuaugga 1200

auuuugaaaa aaaauuucaa aaagaaaaaa auauauauaa uuuaaaacua aaaaaaaaaa 1260

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1320

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa a 1351

<210> 28
<211> 99
<212> PRT
[0050] <213> 智人

<400> 28

Met Lys Val Ser Ala Ala Leu Leu Cys Leu Leu Leu Met Ala Ala Thr
1 5 10 15

Phe Ser Pro Gln Gly Leu Ala Gln Pro Asp Ser Val Ser Ile Pro Ile
20 25 30

Thr Cys Cys Phe Asn Val Ile Asn Arg Lys Ile Pro Ile Gln Arg Leu
35 40 45

Glu Ser Tyr Thr Arg Ile Thr Asn Ile Gln Cys Pro Lys Glu Ala Val
50 55 60

Ile Phe Lys Thr Lys Arg Gly Lys Glu Val Cys Ala Asp Pro Lys Glu
65 70 75 80

Arg Trp Val Arg Asp Ser Met Lys His Leu Asp Gln Ile Phe Gln Asn
85 90 95

Leu Lys Pro

<210> 29
<211> 1525
<212> RNA
<213> 智人

<400> 29

[0051]

cugcuugaag ccuaacuguc caccagaaag gacugcucuu ugggugaguu gaacuucuuc 60

cauuauagaa agaauugaag gcugagaaac ucagccucua ucauguggaa cagcucugac 120

gccaacuucu ccugcuacca ugagucugug cugggcuauc guuauguugc aguuagcugg 180

gggguggugg uggcugugac aggcaccgug ggcaaugugc ucacccuacu ggccuuggcc 240

auccagccca agcuccguac ccgauucaac cugcucauag ccaaccucac acuggcugau 300

cuccucuacu gcacgcuccu ucagcccuuc ucuguggaca ccuaccucca ccugcacugg 360

cgcaccggug ccaccuucug caggguauuu gggcuccucc uuuuugccuc caauucuguc 420

uccauccuga cccucugccu caucgcacug ggacgcuacc uccucauugc ccacccuaag 480

cuuuuucccc aaguuuucag ugccaagggg auagugcugg cacuggugag caccuggguu 540

gugggcgugg ccagcuuugc uccccucugg ccuauuuaua uccugguacc uguagucugc 600

accugcagcu uugaccgcau ccgaggccgg ccuuacacca ccauccucau gggcaucuac 660

uuugugcuug ggcucagcag uguuggcauc uucuauugcc ucauccaccg ccaggucaaa 720

cgagcagcac aggcacugga ccaauacaag uugcgacagg caagcaucca cuccaaccau 780

guggccagga cugaugaggc caugccuggu cguuuccagg agcuggacag cagguuagca 840

ucaggaggac ccagugaggg gauuucaucu gagccaguca gugcugccac cacccagacc 900

cuggaagggg acucaucaga agugggagac cagaucaaca gcaagagagc uaagcagaug 960

gcagagaaaa gcccuccaga agcaucugcc aaagcccagc caauuaaagg agccagaaga 1020

gcuccggauu cuucaucgga auuugggaag gugacucgaa uguguuuugc uguguuccuc 1080

ugcuuugccc ugagcuacau ccccuucuug cugcucaaca uucuggaugc cagaguccag 1140

gcucccggg ugguccacau gcuugcugcc aaccucaccu ggcucaaugg uugcaucaac 1200

ccugugcucu augcagccau gaaccgccaa uuccgccaag cauauggcuc cauuuuaaaa 1260

agagggcccc ggaguuucca uaggcuccau uagaacugug acccuaguca ccagaauuca 1320

ggacugucuc cuccaggacc aaaguggcca gguaauagga gaauagguga aauaacacau 1380

gugggcauuu ucacaacaau cucucccag ccucccaaau caagucucuc caucacuuga 1440

ucaauguuuc agcccuagac ugcccaagga guauuauuaa uuauuaauaa augaauucug 1500

ugcuuuuaaa aaaaaaaaaa aaaaa 1525

<210> 30
<211> 396
<212> PRT
<213> 智人

[0052] <400> 30

Met Trp Asn Ser Ser Asp Ala Asn Phe Ser Cys Tyr His Glu Ser Val
1 5 10 15

Leu Gly Tyr Arg Tyr Val Ala Val Ser Trp Gly Val Val Val Ala Val
20 25 30

Thr Gly Thr Val Gly Asn Val Leu Thr Leu Leu Ala Leu Ala Ile Gln
35 40 45

Pro Lys Leu Arg Thr Arg Phe Asn Leu Leu Ile Ala Asn Leu Thr Leu
50 55 60

Ala Asp Leu Leu Tyr Cys Thr Leu Leu Gln Pro Phe Ser Val Asp Thr
65 70 75 80

Tyr Leu His Leu His Trp Arg Thr Gly Ala Thr Phe Cys Arg Val Phe
85 90 95

Gly Leu Leu Leu Phe Ala Ser Asn Ser Val Ser Ile Leu Thr Leu Cys
100 105 110

Leu Ile Ala Leu Gly Arg Tyr Leu Leu Ile Ala His Pro Lys Leu Phe
115 120 125

Pro Gln Val Phe Ser Ala Lys Gly Ile Val Leu Ala Leu Val Ser Thr
130 135 140

Trp Val Val Gly Val Ala Ser Phe Ala Pro Leu Trp Pro Ile Tyr Ile
145 150 155 160

Leu Val Pro Val Val Cys Thr Cys Ser Phe Asp Arg Ile Arg Gly Arg
165 170 175

Pro Tyr Thr Thr Ile Leu Met Gly Ile Tyr Phe Val Leu Gly Leu Ser
180 185 190

Ser Val Gly Ile Phe Tyr Cys Leu Ile His Arg Gln Val Lys Arg Ala
195 200 205

Ala Gln Ala Leu Asp Gln Tyr Lys Leu Arg Gln Ala Ser Ile His Ser
210 215 220

[0053] Asn His Val Ala Arg Thr Asp Glu Ala Met Pro Gly Arg Phe Gln Glu
225 230 235 240

Leu Asp Ser Arg Leu Ala Ser Gly Gly Pro Ser Glu Gly Ile Ser Ser
245 250 255

Glu Pro Val Ser Ala Ala Thr Thr Gln Thr Leu Glu Gly Asp Ser Ser
260 265 270

Glu Val Gly Asp Gln Ile Asn Ser Lys Arg Ala Lys Gln Met Ala Glu
275 280 285

Lys Ser Pro Pro Glu Ala Ser Ala Lys Ala Gln Pro Ile Lys Gly Ala
290 295 300

Arg Arg Ala Pro Asp Ser Ser Ser Glu Phe Gly Lys Val Thr Arg Met
305 310 315 320

Cys Phe Ala Val Phe Leu Cys Phe Ala Leu Ser Tyr Ile Pro Phe Leu
325 330 335

Leu Leu Asn Ile Leu Asp Ala Arg Val Gln Ala Pro Arg Val Val His

340 345 350

Met Leu Ala Ala Asn Leu Thr Trp Leu Asn Gly Cys Ile Asn Pro Val
355 360 365

Leu Tyr Ala Ala Met Asn Arg Gln Phe Arg Gln Ala Tyr Gly Ser Ile
370 375 380

Leu Lys Arg Gly Pro Arg Ser Phe His Arg Leu His
385 390 395

<210> 31
<211> 839
<212> RNA
<213> 智人

<400> 31

[0054]

gcgugaccag agcgcgcugg cccggcccac ccggggcggu uguggucgcu auauauaagg 60

uggggaggcc gccggcccgu ucgguuccgg gcguuaccau cguccgugcg caccgcccgg 120

cguccagauu uggcaauucu ucgcugaagu caucaugagc uuuuuccaac uccugaugaa 180

aaggaaggaa cucauucccu uggugguguu caugacugug gcggcgggug gagccucauc 240

uuucgcugug uauucucuuu ggaaaaccga ugugauccuu gaucgaaaaa aaaauccaga 300

accuugggaa acuguggacc cuacuguacc ucaaaagcuu auaacaauca accaacaaug 360

gaaacccauu gaagaguugc aaaaugucca aagggugacc aaaugacgag cccucgccuc 420

uuucuucuga agaguacucu auaaaucuag uggaaacauu ucugcacaaa cuagauucug 480

gacaccagug ugcggaaaug cuucugcuac auuuuuaggg uuugucuaca uuuuuuggGC 540

ucuggauaag gaauuaaagg agugcagcaa uaacugcacu gucuaaaagu uugugcuuau 600

uuucuuguaa auuugaauau ugcauauuga aauuuuuguu uaugaucuau gaauguuuuu 660

cuuaaaauuu acaaagcuuu guaaauuaga uuuucuuuaa uaaaaugcca uuugugcaag 720

auuucucaaa gauuagguau auauuuaaau ggaagagaaa auauuuuuau gggagaaaaa 780

uacauuugaa ccaugaaauu ucaucuuuua aauaacaucc aguacagauu ucuguguaa 839

<210> 32
<211> 83
<212> PRT
<213> 智人

<400> 32

Met Ser Phe Phe Gln Leu Leu Met Lys Arg Lys Glu Leu Ile Pro Leu
1 5 10 15

Val Val Phe Met Thr Val Ala Ala Gly Gly Ala Ser Ser Phe Ala Val
20 25 30

Tyr Ser Leu Trp Lys Thr Asp Val Ile Leu Asp Arg Lys Lys Asn Pro
35 40 45

Glu Pro Trp Glu Thr Val Asp Pro Thr Val Pro Gln Lys Leu Ile Thr
50 55 60

Ile Asn Gln Gln Trp Lys Pro Ile Glu Glu Leu Gln Asn Val Gln Arg
65 70 75 80

[0055]

Val Thr Lys

<210> 33
<211> 3553
<212> RNA
<213> 智人

<400> 33

gagccagcgc gguagggcca gagugggaag gccagagcgg gcgucccgc cagugacccc 60

acgccgcccg uccgcgccca acccggccuc cgccgagugu ccaaaccaaa agcgaaagga 120

acccgacccc gcgucccuc cggcggcucc guagucgcgu ccgcuuggag cucgccgggc 180

gccuccgacc cugccgggcc gcuuugugac uucacucguu ucgcaacaag cccgggcagc 240

ccgcgcccca cccacucugg cccggcagcc ucgccgcccg cagccucgcu ccgcuccucg 300

cgcuuccccu cccuccgggg cugggccugc cccggccguc gcggagccuc cccucccacc 360

guccgugagu guacgcgccc ggccgccgcc uccaggcagc ccggagcaac ccggcgcccg 420

gccccgcugg gcgcagcacu ccgucggcgg cggcggcggc gcgaugcugu gcuuccugag 480

gggaauggcu uucguccccu uccucuuggu gaccuggucg ucagccgccu ucauuaucuc 540

cuacgugguc gccgugcucu ccgggcacgu caaccccuuc cucccguaua ucagugauac 600

gggaacaaca ccuccagaga gugguauuuu uggauuuaug auaaacuucu cugcauuucu 660

uggugcagcc acgauguaua caagauacaa aauaguacag aagcaaaauc aaaccugcua 720

uuucagcacu ccuguuuuua acuugguguc uuuagugcuu ggauuggugg gauguuucgg 780

aaugggcauu gucgccaauu uucaggaguu agcugugcca gugguucaug acgggggcgc 840

ucuuuuggcc uuugucugug gugucgugua cacgcuccua caguccauca ucucuuacaa 900

aucauguccc caguggaaca gucucucgac augccacaua cggaugguca ucucugccgu 960

uucuugcgca gcugucaucc ccaugauugu cugugcuuca cuaauuucca uaaccaagcu 1020

[0056]

ggaguggaau ccaagagaaa aggauuaugu auaucacgua gugagugcga ucugugaaug 1080

gacaguggcc uuugguuuua uuuucuacuu ccuaacuuuc auccaagauu uccagagugu 1140

cacccuaagg auauccacag aaaucaaugg ugauauuuga agaaagaaga auucagucuc 1200

acucagugaa ugucgcaggc cauuucuaaa agugcuacag aggacagaca ggguuuugag 1260

gccacccuga uuauugggau gcaucugcag cacauccagg acuugaauuu cauuacgagu 1320

uccuaauagu uguauuucua aagauguguu uccuagagaa uguacagccu uaugacacug 1380

uagugauguu uuuauaauuu ucuaaguaga uuuuuuuaua uuaacaaauu cauauacaga 1440

aaaaauaagg uguuacaaaa aauggagagc ucuuauuuuu guacagauuc ugucguuuuu 1500

guuuuauuug ugugagauuu auggaaauac acuaaaugag uaauucaggu ucaguacauu 1560

uauuacaaag ugaaaucagg ggauauucau uuguaaauuu uauucuuagu gaaugaacug 1620

uauaauuuuu uuuaucagga gagcacuuau aaaauucaau uuauaaagau cauauaccca 1680

aaucauaaag auuuaguuga uacauuaaca cuaagauacu cugauuuuua gccgaacuaa 1740

acaaagugcu ucuacugaga ggccuuuaua ccaccaugua caguaacucu aagugaauac 1800

ggaagaccuu gguuuugaaa uucugccacc uuguuucucc cugcucauga ggucgcaccu 1860

uuugcucuug cugcuaauug cccauucgua guggguguaa ugccaggugg aaugguuuca 1920

acaagucagg ugaaaaccau ccuuuauugu ugcuggcaca acuugauaua uagucugacu 1980

cagaacugaa gcucacaucu caaauucauu ucaugccagu aaauguggca aagagaagaa 2040

aggcccaaga gcgagacaag aagaauggag aaggggcag ccaagaagaa cuucuggguu 2100

caggguacug uuuauuugcu ccuucucuuc augccugugg cuggaugucc cacaacacua 2160

uaagaaauau aagucaagcc cuuuguguua agcaagaacu acagacucca ucuuuucacc 2220

caaaucauga augaccaaua aaaagcaagu uauuccagag gaagaagcag cccuugaaau 2280

guuaaggcuu aggcuugaaa ggugaagagc aggaauucuc ucuuucaaau ccuagagcau 2340

[0057]

aaacccaugu guggccaagu gagaucagcc cucaagggca caugccaagg gcagagcagc 2400

ccauguagac agcuucggag ggcaugggg uguagggagu ucgggguagc uccucauuaa 2460

cuauuuguug ggugaguaaa ggggugaggc ucaguggcag guaccucugc aaugacaagc 2520

ugccucccu cuauguguuu agcauauguu auuagaacau guccgacacc ccuaccgcug 2580

ccauuugggc ccuuuaauaa agccaaguag agaaaucugg caauaaaagg caaauguaag 2640

caugcuuucu uuaagacgca ucauaaaugg uuuucuuuaa gugaauggaa gaguuugaca 2700

gagauacacc uuuguaagaa aacauuaaga augcuggcug gcuguggugg cucacaccug 2760

uauucccagc acuuugggag gccuaggcag gaggauugcu ugagccuggg acuucgagac 2820

cagacuggga aacauggcaa aaucccaucu cuacaacaaa aauacaaaaa uuagccaagu 2880

gcgguggugu gccuguaguc cuaguuacuu gggaggcuga ggugggagaa ucaccugagc 2940

ccaggaggug gaggcugcag ugagccaugc caaugcacuc cagucugggc aacagaguga 3000

gacccugucu caaaaauaaa uaaauaaaua aaugaauaaa gagaaugcua aucauuucug 3060

gguucacugc gacucacugu agugcugggg auccccccuug uaacacugga acugaaagac 3120

agugaugaaa gcuaugucaa gcauucauua uucugaagag gaggagaaau gccacauacc 3180

uuucccaugg gaccuguggu ggaaugaauc cauacuucug ccucacuucg agcagacuuu 3240

uguucucggc gcuccucacg auggaguuuc augcuucauu uucacaucuc ucugcacaau 3300

uagauuggga gcuccuugag ggcagaguac gugccuuaau cuuuaucuuu guaaugccac 3360

aaugaacaga gugccuccug guacacugua ggagcuuaag aaauacucac ugaaugcaug 3420

aaugaaugaa ugaacaaaug aaggaaugac uaaggauguu uguagugcua uaauauagaa 3480

ugggauuuac ucugcuuuac caguuaguuu cauaauaaac aaauagucug uaucgccugg 3540

uaaaaaaaaa aaa 3553

[0058]

<210> 34
<211> 238
<212> PRT
<213> 智人

<400> 34

Met Leu Cys Phe Leu Arg Gly Met Ala Phe Val Pro Phe Leu Leu Val
1 5 10 15

Thr Trp Ser Ser Ala Ala Phe Ile Ile Ser Tyr Val Val Ala Val Leu
20 25 30

Ser Gly His Val Asn Pro Phe Leu Pro Tyr Ile Ser Asp Thr Gly Thr
35 40 45

Thr Pro Pro Glu Ser Gly Ile Phe Gly Phe Met Ile Asn Phe Ser Ala
50 55 60

Phe Leu Gly Ala Ala Thr Met Tyr Thr Arg Tyr Lys Ile Val Gln Lys
65 70 75 80

Gln Asn Gln Thr Cys Tyr Phe Ser Thr Pro Val Phe Asn Leu Val Ser
85 90 95

Leu Val Leu Gly Leu Val Gly Cys Phe Gly Met Gly Ile Val Ala Asn
100 105 110

Phe Gln Glu Leu Ala Val Pro Val Val His Asp Gly Gly Ala Leu Leu
115 120 125

Ala Phe Val Cys Gly Val Val Tyr Thr Leu Leu Gln Ser Ile Ile Ser
130 135 140

Tyr Lys Ser Cys Pro Gln Trp Asn Ser Leu Ser Thr Cys His Ile Arg
145 150 155 160

Met Val Ile Ser Ala Val Ser Cys Ala Ala Val Ile Pro Met Ile Val
165 170 175

Cys Ala Ser Leu Ile Ser Ile Thr Lys Leu Glu Trp Asn Pro Arg Glu
180 185 190

Lys Asp Tyr Val Tyr His Val Val Ser Ala Ile Cys Glu Trp Thr Val
195 200 205

[0059]

Ala Phe Gly Phe Ile Phe Tyr Phe Leu Thr Phe Ile Gln Asp Phe Gln
210 215 220

Ser Val Thr Leu Arg Ile Ser Thr Glu Ile Asn Gly Asp Ile
225 230 235

<210> 35
<211> 1610
<212> RNA
<213> 智人

<400> 35
agagaacaaa acagaaacuc uuggaagcag gaaaggugca ugacucaaag agggaaauuc 60

cugugccaua aaaggauugc ugguguauaa aaugcucuau auaugccaau uaucaauuuc 120

cuuucauguu cagcauuucu acuccuucca agaagagcag caaagcugaa guagcagcag 180

cagcaccagc agcaacagca aaaaacaaac augaguguga agggcauggc uauagccuug 240

gcugugauau ugugugcuac aguuguucaa ggcuucccca uguucaaaag aggacgcugu 300

cuuugcauag gcccuggggu aaaagcagug aaaguggcag auauugagaa agccuccaua 360

auguacccaa guaacaacug ugacaaaaua gaagugauua uuacccugaa agaaaauaaa 420

ggacaacgau gccuaaaucc caaaucgaag caagcaaggc uuauaaucaa aaaaguugaa 480

agaaagaauu uuuaaaaaua ucaaaacaua ugaaguccug gaaaagagca ucugaaaaac 540

cuagaacaag uuuaacugug acuacugaaa ugacaagaau ucuacaguag gaaacugaga 600

cuuuucuaug guuuugugac uuucaacuuu uguacaguua ugugaaggau gaaagguggg 660

ugaaaggacc aaaaacagaa auacagucuu ccugaaugaa ugacaaucag aauuccacug 720

cccaaaggag uccaacaauu aaauggauuu cuaggaaaag cuaccuuaag aaaggcuggu 780

uaccaucgga guuuacaaag ugcuuucacg uucuuacuug uugcauuaua cauucaugca 840

uuucuaggcu agagaaccuu cuagauuuga ugcuuacaac uauucuguug ugacuaugag 900

aacauuucug ucucuagaag ucaucugucu guauugaucu uuaugcuaua uuacuaucug 960

[0060]

ugguuacggu ggagacauug acauuauuac uggagucaag cccuuauaag ucaaaagcau 1020

cuaugugucg uaaaacauuc cucaaacauu uuuucaugca aauacacacu ucuuucccca 1080

aacaucaugu agcacaucaa uauguaggga gacauucuua ugcaucauuu gguuuguuuu 1140

auaaccaauu cauuaaaugu aauucauaaa auguacuaug aaaaaaauua uacgcuaugg 1200

gauacuggca aaagugcaca uauuucauaa ccaaauuagu agcaccaguc uuaauuugau 1260

guuuuucaac uuuuauucau ugagauguuu ugaagcaauu aggauaugug uguuuacugu 1320

acuuuuuguu uugauccguu uguauaaaug auagcaauau cuuggacaca ucugaaauac 1380

aaaauguuuu ugucuaccaa agaaaaaugu ugaaaaauaa gcaaauguau accuagcaau 1440

cacuuuuacu uuuuguaauu cugucucuua gaaaaauaca uaaucuaauc aauuucuuug 1500

uucaugccua uauacuguaa aauuuaggua uacucaagac uaguuuaaag aaucaaaguc 1560

auuuuuuucu cuaauaaacu accacaaccu uucuuuuuua aaaaaaaaaa 1610

<210> 36
<211> 94
<212> PRT
<213> 智人

<400> 36

Met Ser Val Lys Gly Met Ala Ile Ala Leu Ala Val Ile Leu Cys Ala
1 5 10 15

Thr Val Val Gln Gly Phe Pro Met Phe Lys Arg Gly Arg Cys Leu Cys
20 25 30

Ile Gly Pro Gly Val Lys Ala Val Lys Val Ala Asp Ile Glu Lys Ala
35 40 45

Ser Ile Met Tyr Pro Ser Asn Asn Cys Asp Lys Ile Glu Val Ile Ile
50 55 60

Thr Leu Lys Glu Asn Lys Gly Gln Arg Cys Leu Asn Pro Lys Ser Lys
65 70 75 80

[0061]

Gln Ala Arg Leu Ile Ile Lys Lys Val Glu Arg Lys Asn Phe
85 90

<210> 37
<211> 1439
<212> RNA
<213> 智人

<400> 37

agucacauuu cagccacugc ucugagaauu ugugagcagc cccuaacagg cuguuacuuc 60

acuacaacug acgauaugau caucuuaauu uacuuauuuc ucuugcuaug ggaagacacu 120

caaggauggg gauucaagga uggaauuuuu cauaacucca uauggcuuga acgagcagcc 180

gguguguacc acagagaagc acggucuggc aaauacaagc ucaccuacgc agaagcuaag 240

gcggugugug aauuugaagg cggccaucuc gcaacuuaca agcagcuaga ggcagccaga 300

aaaauuggau uucaugucug ugcugcugga uggauggcua agggcagagu uggauacccc 360

auugugaagc cagggcccaa cuguggauuu ggaaaaacug gcauuauuga uuauggaauc 420

cgucucaaua ggagugaaag augggaugcc uauugcuaca acccacacgc aaaggagugu 480

gguggcgucu uuacagaucc aaagcaaauu uuuaaaucuc caggcuuccc aaaugaguac 540

gaagauaacc aaaucugcua cuggcacauu agacucaagu auggucagcg uauucaccug 600

aguuuuuuag auuuugaccu ugaagaugac ccagguugcu uggcugauua uguugaaaua 660

uaugacaguu acgaugaugu ccauggcuuu gugggaagau acuguggaga ugagcuucca 720

gaugacauca ucaguacagg aaaugucaug accuugaagu uucuaaguga ugcuucagug 780

acagcuggag guuuccaaau caaauauguu gcaauggauc cuguauccaa auccagucaa 840

ggaaaaaaua caaguacuac uucuacugga aauaaaaacu uuuuagcugg aagauuuagc 900

cacuuauaaa aaaaaaaaaa aggaugauca aaacacacag uguuuauguu ggaaucuuuu 960

ggaacuccuu ugaucucacu guuauuauua acauuuauuu auuauuuuuc uaaaugugaa 1020

agcaauacau aauuuaggga aaauuggaaa auauaggaaa cuuuaaacga gaaaaugaaa 1080

[0062]

ccucucauaa ucccacugca uagaaauaac aagcguuaac auuuucauau uuuuuucuuu 1140

cagucauuuu ucuauuuugug guauauguau auauguaccu auauguauuu gcauuugaaa 1200

uuuuggaauc cugcucuaug uacaguuuug uauuauacuu uuuaaaucuu gaacuuuaua 1260

aacauuuucu gaaaucauug auuauucuac aaaaacauga uuuuaaacag cuguaaaaua 1320

uucuaugaua ugaauguuuu augcauuauu uaagccuguc ucuauuguug gaauuucagg 1380

ucauuuucau aaauauuguu gcaauaaaua uccuugaaca cacaaaaaaa aaaaaaaaa 1439

<210> 38
<211> 277
<212> PRT
<213> 智人

<400> 38

Met Ile Ile Leu Ile Tyr Leu Phe Leu Leu Leu Trp Glu Asp Thr Gln
1 5 10 15

Gly Trp Gly Phe Lys Asp Gly Ile Phe His Asn Ser Ile Trp Leu Glu
20 25 30

Arg Ala Ala Gly Val Tyr His Arg Glu Ala Arg Ser Gly Lys Tyr Lys
35 40 45

Leu Thr Tyr Ala Glu Ala Lys Ala Val Cys Glu Phe Glu Gly Gly His
50 55 60

Leu Ala Thr Tyr Lys Gln Leu Glu Ala Ala Arg Lys Ile Gly Phe His
65 70 75 80

Val Cys Ala Ala Gly Trp Met Ala Lys Gly Arg Val Gly Tyr Pro Ile
85 90 95

Val Lys Pro Gly Pro Asn Cys Gly Phe Gly Lys Thr Gly Ile Ile Asp
100 105 110

Tyr Gly Ile Arg Leu Asn Arg Ser Glu Arg Trp Asp Ala Tyr Cys Tyr
115 120 125

[0063] Asn Pro His Ala Lys Glu Cys Gly Gly Val Phe Thr Asp Pro Lys Gln
130 135 140

Ile Phe Lys Ser Pro Gly Phe Pro Asn Glu Tyr Glu Asp Asn Gln Ile
145 150 155 160

Cys Tyr Trp His Ile Arg Leu Lys Tyr Gly Gln Arg Ile His Leu Ser
165 170 175

Phe Leu Asp Phe Asp Leu Glu Asp Asp Pro Gly Cys Leu Ala Asp Tyr
180 185 190

Val Glu Ile Tyr Asp Ser Tyr Asp Asp Val His Gly Phe Val Gly Arg
195 200 205

Tyr Cys Gly Asp Glu Leu Pro Asp Asp Ile Ile Ser Thr Gly Asn Val
210 215 220

Met Thr Leu Lys Phe Leu Ser Asp Ala Ser Val Thr Ala Gly Gly Phe
225 230 235 240

Gln Ile Lys Tyr Val Ala Met Asp Pro Val Ser Lys Ser Ser Gln Gly

245 250 255

Lys Asn Thr Ser Thr Thr Ser Thr Gly Asn Lys Asn Phe Leu Ala Gly
260 265 270

Arg Phe Ser His Leu
275

<210> 39
<211> 3188
<212> RNA
<213> 智人

<400> 39
gggcggggcu gggcgcaggc agucucccgc cgccgccgcc gcugccggac gcgcagagcg 60

aggggcggcu ggaccgacgg cugccgggcc gagcgcacag agucgcggcg caggggcgu 120

ccccggccgg gacgcggguc gcgucguugu ccuccgcgag cguccggauu gcaggcuguc 180

ugucccccaga ccccagagca cguccggcac caccaugacu gggcuguuga agaggaaauu 240

[0064]

ugaccagcug gaugaggaca acuccucggu cuccuccucc uccucuuccu cugggugcca 300

gucucgcucc ugcucccccaa gcucuucugu cucccgugcc ugggacucag aggaggaagg 360

ccccugggau cagaugcccc ugccugaccg ugacuucugc ggccccagaa guuucacccc 420

ccugucuauc cugaagcggg cucgccggga gcgcccaggc cguguagccu uugaugggau 480

caccgucuuc uacuuccccc gcugccaggg cuucaccagu gugcccagcc gugguggcug 540

uacucugggu auggcccuuc gccacagugc uugccgucgc uucucuuugg cugaguuugc 600

gcaggagcaa gcccgugcac ggcacgagaa gcuccgccag cgcuugaaag aggagaaguu 660

ggagaugcug caguggaagc uuucggcagc ugggguaccc caggcagagg cagggcugcc 720

accuguggug gaugccauug augacgccuc uguggaggag gacuuggcag ucgcuguggc 780

agguggccgg uuggaagaag ugagcuuccu acagcccuac ccagcccggc gacgucgagc 840

ucugcugagg gcuucaggug ugcgaaggau cgaucgggag gagaagcggg agcugcaggc 900

acugcgccaa ucccgggagg auuguggcug ucacugcgau aggaucugcg acccugagac 960

cugcagcugc agccuggcag gcaucaagug ccagauggac cacacagcau uccccugugg 1020

cugcugcagg gagggcugug agaaccccau gggccgugug gaauuuaauc aggcaagagu 1080

ucagacccau uucauccaca cacucacccg ccugcaguug gaacaggagg cugagagcuu 1140

uagggagcug gaggccccug cccagggcag cccacccagc ccuggugagg aggcccuggu 1200

cccuacuuuc ccacuggcca agccccccau gaacaaugag cugggagaca acagcugcag 1260

cagcgacaug acugauucuu cuacagcauc uucaucagca ucgggcacua gugaggcucc 1320

ugacugcccc acccacccag gccugccugg cccuggcuuc cagccuggcg uugaugauga 1380

cagccuggca cgcaucuuga guuucaguga cucugacuuc ggugggggagg aggaggaaga 1440

ggaggaaggg agcgugggga accuggacaa ccucagcugc uuccauccag cugacaucuu 1500

ugguacuagu gacccuggug gccuggccag cuggacccac agcuauucug gcuguagcuu 1560

[0065]

cacaucaggc guccuggaug agaaugccaa ccuggaugcc agcugcuucc uaaauggugg 1620

ccuugaaggg ucaagggaag gcagccuucc uggcaccuca gugccaccca gcauggacgc 1680

uggccggagu agcucagugg aucucagcuu gucuucuugu gacuccuuug aguuacucca 1740

ggcucugcca gauuauaguc uggggccuca cuacacauca cagaaggugu cugacagccu 1800

ggacaacauc gaggcaccuc acuucccccu gccuggccug ucuccaccug gggaugccag 1860

caguugcuuc cuggaguccc ucaugggcuu cuccgagcca gccgccgaag cccuagaucc 1920

cuuuauugac agccaguuug aggacacugu cccagcaucu cuaauggagc cugugccggu 1980

gugaggacca ggaugucuuu ucccagcccc aagagaccug uugcugcuuu cuuguaauua 2040

uggggcuccc cagagucugc guaacagucu cccacuggcu ggcucaccca caggugccau 2100

gugcacacuc cugguuuuca aacaauucuc uggauuuauu uauuuguuuu aacuuuucug 2160

ugcugaagag aggacugggg ggagggggcu uccccuuuca gcugcccggc cccccacacc 2220

cacagcuugc ucuucuaucu ccacaacgug agccuggaag aggagaaaau guggcuccuc 2280

uggagcuugg cagaccacuu uucggucuuu gcgugauguu ccuuagccca aagacgguga 2340

gacagggcug aaaucaggug gcuucugcca cccugagccc uagacccaug gguggcuaaa 2400

uccacuggac ugugaagacu auaauuuauu uccauaauuu auuuggagau ugaggaggcu 2460

uugguugcac uucuuuggcu ggugggguaau gccaggggug ggggugggcac aggcccucaa 2520

gagccccuuu ugccuuguag uccuacaccu ugcccugccu gggcuuuggu gcagacuagg 2580

uguggauuug agcucuguga ucuaugucug cugccuggcu ccuagauggc ucugugggca 2640

ggugcuggcc aaggacauca ucuaggcagg gggagagccu gggcugaaca gcugugacca 2700

aaacucccuu cugccccacc cugcccccuc cacuuccugc ccucuguucc aucuuccccc 2760

uucccaaagg ccacagccuu uauuccaggc ccagggaugu aggaggggga aggaggaaac 2820

aggaagccca gagagggcaa agggccuacc ucggggcgcg aaccaugccc cagacuauua 2880

[0066]

ucucagggcu uucugggcac ugcacuucag cguggcccac cugcccaugc ccugaggcca 2940

guuggcgagg gguggcuccu gaggguuuuu auacccuuug uuugcuaaug uuuaauuuug 3000

caucauaauu ucuacauugu cccugagugu cagaacuaua auuuauucca uuucucucug 3060

ugucugugcc aagaaacgca ggcucugggc cugccccuug cccaggaggc cuugccagcc 3120

ugugugcuug ugggaacacc uuguaccuga gcuuacaggu accaauaaag aggcuuuauu 3180

uuuagcaa 3188

<210> 40
<211> 589
<212> PRT
<213> 智人

<400> 40

Met Thr Gly Leu Leu Lys Arg Lys Phe Asp Gln Leu Asp Glu Asp Asn
1 5 10 15

Ser Ser Val Ser Ser Ser Ser Ser Ser Ser Gly Cys Gln Ser Arg Ser
20 25 30

Cys Ser Pro Ser Ser Ser Val Ser Arg Ala Trp Asp Ser Glu Glu Glu
35 40 45

Gly Pro Trp Asp Gln Met Pro Leu Pro Asp Arg Asp Phe Cys Gly Pro
50 55 60

Arg Ser Phe Thr Pro Leu Ser Ile Leu Lys Arg Ala Arg Arg Glu Arg
65 70 75 80

Pro Gly Arg Val Ala Phe Asp Gly Ile Thr Val Phe Tyr Phe Pro Arg
85 90 95

Cys Gln Gly Phe Thr Ser Val Pro Ser Arg Gly Gly Cys Thr Leu Gly
100 105 110

Met Ala Leu Arg His Ser Ala Cys Arg Arg Phe Ser Leu Ala Glu Phe
115 120 125

[0067]

Ala Gln Glu Gln Ala Arg Ala Arg His Glu Lys Leu Arg Gln Arg Leu
130 135 140

Lys Glu Glu Lys Leu Glu Met Leu Gln Trp Lys Leu Ser Ala Ala Gly
145 150 155 160

Val Pro Gln Ala Glu Ala Gly Leu Pro Pro Val Val Asp Ala Ile Asp
165 170 175

Asp Ala Ser Val Glu Glu Asp Leu Ala Val Ala Val Ala Gly Gly Arg
180 185 190

Leu Glu Glu Val Ser Phe Leu Gln Pro Tyr Pro Ala Arg Arg Arg Arg
195 200 205

Ala Leu Leu Arg Ala Ser Gly Val Arg Arg Ile Asp Arg Glu Glu Lys
210 215 220

Arg Glu Leu Gln Ala Leu Arg Gln Ser Arg Glu Asp Cys Gly Cys His
225 230 235 240

Cys Asp Arg Ile Cys Asp Pro Glu Thr Cys Ser Cys Ser Leu Ala Gly
245 250 255

Ile Lys Cys Gln Met Asp His Thr Ala Phe Pro Cys Gly Cys Cys Arg
260 265 270

Glu Gly Cys Glu Asn Pro Met Gly Arg Val Glu Phe Asn Gln Ala Arg
275 280 285

Val Gln Thr His Phe Ile His Thr Leu Thr Arg Leu Gln Leu Glu Gln
290 295 300

Glu Ala Glu Ser Phe Arg Glu Leu Glu Ala Pro Ala Gln Gly Ser Pro
305 310 315 320

Pro Ser Pro Gly Glu Glu Ala Leu Val Pro Thr Phe Pro Leu Ala Lys
325 330 335

Pro Pro Met Asn Asn Glu Leu Gly Asp Asn Ser Cys Ser Ser Asp Met
340 345 350

Thr Asp Ser Ser Thr Ala Ser Ser Ser Ala Ser Gly Thr Ser Glu Ala
355 360 365

[0068] Pro Asp Cys Pro Thr His Pro Gly Leu Pro Gly Pro Gly Phe Gln Pro
370 375 380

Gly Val Asp Asp Asp Ser Leu Ala Arg Ile Leu Ser Phe Ser Asp Ser
385 390 395 400

Asp Phe Gly Gly Glu Glu Glu Glu Glu Glu Glu Gly Ser Val Gly Asn
405 410 415

Leu Asp Asn Leu Ser Cys Phe His Pro Ala Asp Ile Phe Gly Thr Ser
420 425 430

Asp Pro Gly Gly Leu Ala Ser Trp Thr His Ser Tyr Ser Gly Cys Ser
435 440 445

Phe Thr Ser Gly Val Leu Asp Glu Asn Ala Asn Leu Asp Ala Ser Cys
450 455 460

Phe Leu Asn Gly Gly Leu Glu Gly Ser Arg Glu Gly Ser Leu Pro Gly
465 470 475 480

Thr Ser Val Pro Pro Ser Met Asp Ala Gly Arg Ser Ser Ser Val Asp

485 490 495

Leu Ser Leu Ser Ser Cys Asp Ser Phe Glu Leu Leu Gln Ala Leu Pro
500 505 510

Asp Tyr Ser Leu Gly Pro His Tyr Thr Ser Gln Lys Val Ser Asp Ser
515 520 525

Leu Asp Asn Ile Glu Ala Pro His Phe Pro Leu Pro Gly Leu Ser Pro
530 535 540

Pro Gly Asp Ala Ser Ser Cys Phe Leu Glu Ser Leu Met Gly Phe Ser
545 550 555 560

Glu Pro Ala Ala Glu Ala Leu Asp Pro Phe Ile Asp Ser Gln Phe Glu
565 570 575

Asp Thr Val Pro Ala Ser Leu Met Glu Pro Val Pro Val
580 585

<210> 41

[0069] <211> 2228

<212> RNA

<213> 智人

<400> 41

caccggacaa acgucucugg agucucucca augagcaaga aagcaagucg gggguagggg 60

aggggccuca caccaggggg ugggcgcagu cccuccucca gcuccuucac ccuccaguag 120

ucucgugggu ccccgagcgc cagcgcggga accgggaaaa ggaaaccgug uuguguacgu 180

aagauucagg aaacgaaacc aggagccgcg gguguuggcg caaagguuac ucccagaccc 240

uuuuccggcu gacuucugag aagguugcgc agcagcugug cccggcaguc uagaggcgca 300

gaagaggaag ccaucgccug gccccggcuc ucuggaccuu gucucgcucg ggagcggaaa 360

cagcggcagc cagagaacug uuuuaaucau ggacaaacaa aacucacaga ugaaugcuuc 420

ucacccggaa acaaacuugc caguugggua uccuccucag uauccaccga cagcauucca 480

aggaccucca ggauauagug gcuacccugg gccccagguc agcuacccac ccccaccagc 540

cggccauuca gguccuggcc cagcuggcuu uccuguccca aaucagccag uguauaauca 600

gccaguauau aaucagccag uuggagcugc agggguacca uggaugccag cgccacagcc 660

uccauuaaac uguccaccug gauuagaaua uuuaagucag auagaucaga uacugauuca 720

ucagcaaauu gaacuucugg aaguuuuaac agguuuugaa acuaauaaca aauaugaaau 780

uaagaacagc uuuggacaga ggguuuacuu ugcagcggaa gauacugauu gcuguacccg 840

aaauugcugu gggccaucua gaccuuuuac cuugaggauu auugauaaua ugggucaaga 900

agucauaacu cuggagagac cacuaagaug uagcagcugu uguugucccu gcugccuuca 960

ggagauagaa auccaagcuc cuccuggugu accaauaggu uauguuauuc agacuuggca 1020

cccaugucua ccaaaguuua caauucaaaa ugagaaaaga gaggauguac uaaaaauaag 1080

ugguccaugu guugugugca gcuguugugg agauguugau uuugagauua aaucucuuga 1140

ugaacagugu gugguuggca aaauuuccaa gcacuggacu ggaauuuuga gagaggcauu 1200

[0070]

uacagacgcu gauaacuuug gaauccaguu cccuuuagac cuugauguua aaaugaaagc 1260

uguaaugauu ggugccuguu uccucauuga cuucauguuu uuugaaagca cuggcagcca 1320

ggaacaaaaa ucaggagugu gguaguggau uagugaaagu cuccucagga aaucugaagu 1380

cuguauauug auugagacua ucuaaacuca uaccuguaug aauuaagcug uaaggccugu 1440

agcucugguu guauacuuuu gcuuuucaaa uuauaguuua ucuucuguau aacugauuua 1500

uaaagguuuu uguacauuuu uuaauacuca uugucaauuu gagaaaaagg acauaugagu 1560

uuuugcauuu auuaaugaaa cuuccuuuga aaaacugcuu ugaauuauga ucucugauuc 1620

auuguccauu uuacuaccaa auauuaacua aggccuuauu aauuuuuaua uaaauuauau 1680

cuuguccuau uaaaucuagu uacaauuuau uucaugcaua agagcuaaug uuauuuugca 1740

aaugccauau auucaaaaaa gcucaaagau aauuuucuuu acuauuaugu ucaaauaaua 1800

uucaauaugc auauuaucuu uaaaaaguua aauguuuuuu uaaucuucaa gaaaucaugc 1860

uacacuuaac uucuccuaga agcuaaucua uaccauaaua uuuucauauu cacaagauau 1920

uaaauuacca auuuucaaau uauuguuagu aaagaacaaa augauucucu cccaaagaaa 1980

gacacauuuu aaauacuccu ucacucuaaa acucugguau uauaacuuuu gaaaguuaau 2040

auuucuacau gaaauguuua gcucuuacac ucuauccuuc cuagaaaaug guaauugaga 2100

uuacucagau auuaauuaaa uacaauauca uauauauauu cacagaguau aaaccuaaau 2160

aaugaucuau uagauucaaa uauuugaaau aaaaacuuga uuuuuuugua aaaaaaaaaa 2220

aaaaaaaa 2228

<210> 42
<211> 318
<212> PRT
<213> 智人

<400> 42

[0071]

```
Met Asp Lys Gln Asn Ser Gln Met Asn Ala Ser His Pro Glu Thr Asn
1               5                  10                  15

Leu Pro Val Gly Tyr Pro Pro Gln Tyr Pro Pro Thr Ala Phe Gln Gly
            20                  25                  30

Pro Pro Gly Tyr Ser Gly Tyr Pro Gly Pro Gln Val Ser Tyr Pro Pro
        35                  40                  45

Pro Pro Ala Gly His Ser Gly Pro Gly Pro Ala Gly Phe Pro Val Pro
    50                  55                  60

Asn Gln Pro Val Tyr Asn Gln Pro Val Tyr Asn Gln Pro Val Gly Ala
65                  70                  75                  80

Ala Gly Val Pro Trp Met Pro Ala Pro Gln Pro Pro Leu Asn Cys Pro
                85                  90                  95

Pro Gly Leu Glu Tyr Leu Ser Gln Ile Asp Gln Ile Leu Ile His Gln
            100                 105                 110

Gln Ile Glu Leu Leu Glu Val Leu Thr Gly Phe Glu Thr Asn Asn Lys
```

115 120 125

Tyr Glu Ile Lys Asn Ser Phe Gly Gln Arg Val Tyr Phe Ala Ala Glu
130 135 140

Asp Thr Asp Cys Cys Thr Arg Asn Cys Cys Gly Pro Ser Arg Pro Phe
145 150 155 160

Thr Leu Arg Ile Ile Asp Asn Met Gly Gln Glu Val Ile Thr Leu Glu
165 170 175

Arg Pro Leu Arg Cys Ser Ser Cys Cys Cys Pro Cys Cys Leu Gln Glu
180 185 190

Ile Glu Ile Gln Ala Pro Pro Gly Val Pro Ile Gly Tyr Val Ile Gln
195 200 205

Thr Trp His Pro Cys Leu Pro Lys Phe Thr Ile Gln Asn Glu Lys Arg
210 215 220

Glu Asp Val Leu Lys Ile Ser Gly Pro Cys Val Val Cys Ser Cys Cys
225 230 235 240

[0072]

Gly Asp Val Asp Phe Glu Ile Lys Ser Leu Asp Glu Gln Cys Val Val
245 250 255

Gly Lys Ile Ser Lys His Trp Thr Gly Ile Leu Arg Glu Ala Phe Thr
260 265 270

Asp Ala Asp Asn Phe Gly Ile Gln Phe Pro Leu Asp Leu Asp Val Lys
275 280 285

Met Lys Ala Val Met Ile Gly Ala Cys Phe Leu Ile Asp Phe Met Phe
290 295 300

Phe Glu Ser Thr Gly Ser Gln Glu Gln Lys Ser Gly Val Trp
305 310 315

<210> 43
<211> 2158
<212> RNA
<213> 智人

<400> 43

auauucuaca ucuaucggag cugaacuucc uaaaagacaa aguguuuauc uuucaagauu 60

cauucucccu gaaucuuacc aacaaaacac uccugaggag aaagaaagag agggagggag 120

agaaaaagag agagagagaa acaaaaaacc aaagagagag aaaaaaugaa uucaucuaaa 180

ucaucugaaa cacaaugcac agagagagga ugcuucucuu cccaaauguu cuuauggacu 240

guugcuggga uccccauccu auuucucagu gccuguuuca ucaccagaug uguugugaca 300

uuucgcaucu uucaaaccug ugaugagaaa aaguuucagc uaccugagaa uuucacagag 360

cucuccugcu acaauuaugg aucagguuca gucaagaauu guuguccauu gaacugggaa 420

uauuuucaau ccagcugcua cuucuuuucu acugacacca uuuccugggc guuaaguuua 480

aagaacugcu cagccauggg ggcucaccug gugguuauca acucacagga ggagcaggaa 540

uuccuuuccu acaagaaacc uaaaaugaga gaguuuuuua uuggacuguc agaccagguu 600

gucgaggguc aguggcaaug gguggacggc acaccuuuga caaagucucu gagcuucugg 660

[0073]

gauguagggg agcccaacaa cauagcuacc cuggaggacu gugccaccau gagagacucu 720

ucaaacccaa ggcaaaauug gaaugaugua accuguuucc ucaauuauuu ucggauuugu 780

gaaaugguag gaauaaaucc uuugaacaaa ggaaaaucuc uuuaagaaca gaaggcacaa 840

cucaaaugug uaaagaagga agagcaagaa cauggccaca cccaccgccc cacacgagaa 900

auuugugcgc ugaacuucaa aggacuucau aaguauuugu uacucugaua uaaauaaaaa 960

uaaguaguuu uaaauguuau aauucauguu acuggcugaa gugcauuuuc ucucuacguu 1020

agucucaggu ccucuuccca gaauuuacaa agcaauucac uaccuuuugc uacauuugcc 1080

ucauuuuuua guguucguau gaaaguacag ggacacggag ccaagacaga gucuagcaaa 1140

gaaggggauu uuggaaggug ccuuccaaaa aucuccugaa uccgggcucu guagcagguc 1200

cucuucuuuc uagcuucuga caagucuguc uucucuucuu gguuucauac cguucuuauc 1260

uccugcccaa gcauauaucg ucucuuuacu ccccuguaua augaguaaga agcuucuuca 1320

agucaugaaa cuuauuccug cucagaauac cgguguggcc uuucuggcua caggccucca 1380

cugcaccuuc uuagggaagg gcaugccagc caucagcucc aaacaggcug uaaccaaguc 1440

cacccauccc uggggcuucc uuugcucugc cuuauuuuca auugacugaa uggaucucac 1500

cagauuuugu aucuauugcu cagcuaggac ccgaguccaa uagucaauuu auucuaagcg 1560

aacauucauc uccacacuuu ccugucucaa gcccauccau uauuucuuaa cuuuuauuuu 1620

agcuuucggg gguacauguu aaaggcuuuu uauauaggua aacucauguc guggagguuu 1680

guuguacaga uuauuucauc acccagguau uaagcccagu gccuaauauu guuuuuuucg 1740

gcuccucucc cuccuccuac cuuccgcccu caaguagacu ccagugucug uuauucccuu 1800

cuuuguguuu augaauucuc aucauuuagc ucccacuuau aagugaggac augcaguauu 1860

ugguuuucug uucccauguu ugcuaaggau aauggucucc aguucuaccg auguucccac 1920

aaaagacaua aucuucuuuu uuaaggcugc uuaguauucc augguaucua uguaucacau 1980

[0074]

uuucucuauc caaucuauug uugacucaca uuuagauuga uuccauguuu uugcuauugu 2040

gaauagugcu gcaaugaaca uucgugugca ugugucuuua ugguagaaag auuuauauuu 2100

cucugaguau guauccagua auagcccauu cauuuauugc auaaaauucu accaauac 2158

<210> 44
<211> 219
<212> PRT
<213> 智人

<400> 44

Met Asn Ser Ser Lys Ser Ser Glu Thr Gln Cys Thr Glu Arg Gly Cys
1 5 10 15

Phe Ser Ser Gln Met Phe Leu Trp Thr Val Ala Gly Ile Pro Ile Leu
20 25 30

Phe Leu Ser Ala Cys Phe Ile Thr Arg Cys Val Val Thr Phe Arg Ile
35 40 45

Phe Gln Thr Cys Asp Glu Lys Lys Phe Gln Leu Pro Glu Asn Phe Thr
50 55 60

Glu Leu Ser Cys Tyr Asn Tyr Gly Ser Gly Ser Val Lys Asn Cys Cys
65 70 75 80

Pro Leu Asn Trp Glu Tyr Phe Gln Ser Ser Cys Tyr Phe Phe Ser Thr
85 90 95

Asp Thr Ile Ser Trp Ala Leu Ser Leu Lys Asn Cys Ser Ala Met Gly
100 105 110

Ala His Leu Val Val Ile Asn Ser Gln Glu Glu Gln Glu Phe Leu Ser
115 120 125

Tyr Lys Lys Pro Lys Met Arg Glu Phe Phe Ile Gly Leu Ser Asp Gln
130 135 140

Val Val Glu Gly Gln Trp Gln Trp Val Asp Gly Thr Pro Leu Thr Lys
145 150 155 160

[0075]

Ser Leu Ser Phe Trp Asp Val Gly Glu Pro Asn Asn Ile Ala Thr Leu
165 170 175

Glu Asp Cys Ala Thr Met Arg Asp Ser Ser Asn Pro Arg Gln Asn Trp
180 185 190

Asn Asp Val Thr Cys Phe Leu Asn Tyr Phe Arg Ile Cys Glu Met Val
195 200 205

Gly Ile Asn Pro Leu Asn Lys Gly Lys Ser Leu
210 215

<210> 45
<211> 1922
<212> RNA
<213> 智人

<400> 45
cuuaucugau gcugugcauu agacagcaca cugcugacug uuuucaguug uuucuguaac 60

agcagaaagu gcacucacua ggaguaguca gaauucaaaa ugcucaagag aaagccaucc 120

aauguuucag agaaggagaa acaucaaaaa ccaaagcgaa gcagcaguuu ugggaauuuc 180

gaucguuuuc ggaauaauuc uuuaucaaaa ccagaugauu caacugaggc acaugaagga 240

gaucccacaa auggaagugg agaacaaagu aaaacuucaa auaauggagg cgguuugggu 300

aaaaaaauga gagcuauuuc auggacaaug aagaaaaaag uggguaaaaa guacaucaaa 360

gcccuuucug aggaaaagga ugaggaagau ggagagaaug cccacccaua uagaaacagu 420

gacccuguga uugggaccca cacagagaag gugucccuca aagccaguga cuccauggau 480

agucucuaca guggacagag cucaucaagu ggcauaacaa gcuguucaga ugguacaagu 540

aaccgggaca gcuuucgacu ggaugacgau ggccccuauu caggaccauu cuguggccgu 600

gccagagugc auacggauuu cacgccaagu cccuaugaca cugacucccu caaaaucaag 660

aaaggagaca ucauagacau uauuugcaaa acaccaaugg ggauguggac aggaauguug 720

aacaauaaag ugggaaacuu caaauucauu uauguggaug ucaucucaga agaggaagca 780

gcccccaaga aaauaaaggc aaaccgaagg aguaacagca aaaaauccaa gacucugcag 840

[0076]

gaguuccuag agaggauuca ucugcaggaa uacaccucaa cacuuuugcu caaugguuau 900

gagacucuag aagauuuaaa agauauaaaa gagagucacc ucauugaauu aaauauugaa 960

aacccagaug acagaagaag guuacuauca gcugcugaaa acuuccuuga agaagaaauu 1020

auucaagagc aagaaaauga accugagccc cuauccuuga gcucagacau cuccuuaaau 1080

aagucacagu uagaugacug cccaagggac ucugguugcu auaucucauc aggaaauuca 1140

gauaauggca aagaggaucu ggagucugaa aaucugucug acaugguaca uaagauuauu 1200

aucacagagc caagugacug aacacgcauu cccaacuaua uaucuacaga ugcauuccau 1260

uuuaacucuu cuugagcuaa aacgucaaau aggagaggaa gauaagauaa auauuuguaa 1320

auaaaaccua aaguuuaaau guuuuaaucu gaauaauugu acauaaaauu uuguaucucu 1380

aacauuccaa auuacuguca auaaaauaua uauuuauuau uuuaaaugcu auguguuaau 1440

auuucacuug cuuguauuag aaaggcaaaa uguaagacuu ugguaugugu gacauaugcu 1500

uuauuuggcu uuauuuuaca aguacaguau cugcaaaaaa caaaguaacc uuuuuucaua 1560

ccugccaguu uugaauuuau auauguuauu gaacaaauag uaauagagga uucgcuguug 1620

aaacaaguug uccaagcaau guuauauuca uuuuuauacu uauugggaaa gugugaguua 1680

auauuggaca cauuuuaucc ugauccacag uggaguuuua guaauuauau uuuguugauu 1740

ucuucauuuu guuuucuggu auaaaaguag agauaaugug uagucacuuc ugauuuagug 1800

aaaccaauug uaauaauugu ggaaauguuu ugucuuuaag uguaaauauu uuaaaauuug 1860

acauacccua auguuaauaa uaaaaagaac uauuugcaua uugcaaaaaa aaaaaaaaaa 1920

aa 1922

<210> 46
<211> 373
<212> PRT
<213> 智人

[0077] <400> 46

Met Leu Lys Arg Lys Pro Ser Asn Val Ser Glu Lys Glu Lys His Gln
1 5 10 15

Lys Pro Lys Arg Ser Ser Ser Phe Gly Asn Phe Asp Arg Phe Arg Asn
20 25 30

Asn Ser Leu Ser Lys Pro Asp Asp Ser Thr Glu Ala His Glu Gly Asp
35 40 45

Pro Thr Asn Gly Ser Gly Glu Gln Ser Lys Thr Ser Asn Asn Gly Gly
50 55 60

Gly Leu Gly Lys Lys Met Arg Ala Ile Ser Trp Thr Met Lys Lys Lys
65 70 75 80

Val Gly Lys Lys Tyr Ile Lys Ala Leu Ser Glu Glu Lys Asp Glu Glu
85 90 95

Asp Gly Glu Asn Ala His Pro Tyr Arg Asn Ser Asp Pro Val Ile Gly
100 105 110

Thr His Thr Glu Lys Val Ser Leu Lys Ala Ser Asp Ser Met Asp Ser
115 120 125

Leu Tyr Ser Gly Gln Ser Ser Ser Ser Gly Ile Thr Ser Cys Ser Asp
130 135 140

Gly Thr Ser Asn Arg Asp Ser Phe Arg Leu Asp Asp Asp Gly Pro Tyr
145 150 155 160

Ser Gly Pro Phe Cys Gly Arg Ala Arg Val His Thr Asp Phe Thr Pro
165 170 175

Ser Pro Tyr Asp Thr Asp Ser Leu Lys Ile Lys Lys Gly Asp Ile Ile
180 185 190

Asp Ile Ile Cys Lys Thr Pro Met Gly Met Trp Thr Gly Met Leu Asn
195 200 205

Asn Lys Val Gly Asn Phe Lys Phe Ile Tyr Val Asp Val Ile Ser Glu
210 215 220

[0078] Glu Glu Ala Ala Pro Lys Lys Ile Lys Ala Asn Arg Arg Ser Asn Ser
225 230 235 240

Lys Lys Ser Lys Thr Leu Gln Glu Phe Leu Glu Arg Ile His Leu Gln
245 250 255

Glu Tyr Thr Ser Thr Leu Leu Leu Asn Gly Tyr Glu Thr Leu Glu Asp
260 265 270

Leu Lys Asp Ile Lys Glu Ser His Leu Ile Glu Leu Asn Ile Glu Asn
275 280 285

Pro Asp Asp Arg Arg Arg Leu Leu Ser Ala Ala Glu Asn Phe Leu Glu
290 295 300

Glu Glu Ile Ile Gln Glu Gln Glu Asn Glu Pro Glu Pro Leu Ser Leu
305 310 315 320

Ser Ser Asp Ile Ser Leu Asn Lys Ser Gln Leu Asp Asp Cys Pro Arg
325 330 335

Asp Ser Gly Cys Tyr Ile Ser Ser Gly Asn Ser Asp Asn Gly Lys Glu

340 345 350

Asp Leu Glu Ser Glu Asn Leu Ser Asp Met Val His Lys Ile Ile Ile
355 360 365

Thr Glu Pro Ser Asp
370

<210> 47
<211> 3776
<212> RNA
<213> 智人

<400> 47

[0079]

gggacugugu uaagaaccaa gggcauauaa agacagaugg gaggagaccc uggccgggga 60

gaggaagaag caucuacaua gguacuaagu accauucgcu aauucagcuu agagaacuau 120

caacacagga caaugcaagc ccaugagcug uuccgguauu uucgaaugcc agagcugguu 180

gacuuccgac aguacgugcg uacucuuccg accaacacgc uuaugggcuu cggagcuuuu 240

gcagcacuca ccaccuucug guacgccacg agacccaaac cccugaagcc gccaugcgac 300

cucuccaugc agucagugga aguggcgggu agugguggug cacgaagauc cgcacuacuu 360

gacagcgacg agcccuuggu guauuucuau gaugauguca caacauuaua cgaagguuuc 420

cagaggggaa uacagguguc aaauaauggc ccuuguuuag gcucucggaa accagaccaa 480

cccuaugaau ggcuuucaua uaaacagguu gcagaauugu cggagugcau aggcucagca 540

cugauccaga agggcuucaa gacugcccca gaucaguuca uuggcaucuu ugcucaaaau 600

agaccugagu gggugauuau ugaacaagga ugcuuugcuu auucgauggu gaucguucca 660

cuuuaugaua cccuuggaaa ugaagccauc acguacauag ucaacaaagc ugaacucucu 720

cugguuuuug uugacaagcc agagaaggcc aaacucuuau uagagggugu agaaaauaag 780

uuaauaccag gccuuaaaau cauaguuguc auggaugccu acggcaguga acugguggaa 840

cgaggccaga gguguggggu ggaagucacc agcaugaagg cgauggagga ccugggaaga 900

gccaacagac ggaagcccaa gccuccagca ccugaagauc uugcaguaau uuguuucaca 960

aguggaacua caggcaaccc caaaggagca auggucacuc accgaaacau agugagcgau 1020

uguucagcuu uugugaaagc aacagagaau acagucaauc cuugcccaga ugauacuuug 1080

auaucuuucu ugccucucgc ccauauguuu gagagaguug uagagugugu aaugcugugu 1140

cauggagcua aaaucggauu uuuccaagga gauaucaggc ugcucaugga ugaccucaag 1200

gugcuucaac ccacugucuu ccccgugguu ccaagacugc ugaaccggau guuugaccga 1260

auuuucggac aagcaaacac cacgcugaag cgauggcucu uggacuuugc cuccaagagg 1320

aaagaagcag agcuucgcag cggcaucauc agaaacaaca gccuguggga ccggcugauc 1380

uuccacaaag uacagucgag ccugggcgga agaguccggc ugauggugac aggagccgcc 1440

ccggugucug ccacugugcu gacguuccuc agagcagccc ugggcuguca guuuuaugaa 1500

ggauacggac agacagagug cacugccggg ugcugccuga ccaugccugg agacuggacc 1560

[0080]

gcaggccaug uuggggcccc gaugccgugc aauuugauaa aacuuguuga uguggaagaa 1620

augaauuaca uggcugccga gggcgagggc gaggugugug ugaaagggcc aaauguauuu 1680

cagggcuacu ugaaggaccc agcgaaaaca gcagaagcuu uggacaaaga cggcugguua 1740

cacacagggg acauuggaaa augguuacca aauggcaccu ugaaaauuau cgaccggaaa 1800

aagcacauau uuaagcuggc acaaggagaa uacauagccc cugaaaagau ugaaaauauc 1860

uacaugcgaa gugagccugu ugcucaggug uuuguccacg gagaaagccu gcaggcauuu 1920

cucauugcaa uuugugguacc agauguugag acauuauguu ccugggccca aaagagagga 1980

uuugaagggu cguuugagga acugugcaga aauaaggaug ucaaaaaagc uauccucgaa 2040

gauaugguga gacuugggaa ggauucuggu cugaaaccau uugaacaggu caaaggcauc 2100

acauugcacc cugaauuauu uucuaucgac aauggccuuc ugacuccaac aaugaaggcg 2160

aaaaggccag agcugcggaa cuauuucagg ucgcagauag augaccucua uuccacuauc 2220

aagguuuagu gugaagaaga aagcucagag gaaauggcac aguuccacaa ucucuucucc 2280

ugcugauggc cuucauguug uuaauuuuga auacagcaag uguagggaag gaagcguucg 2340

uguuugacuu guccauucgg gguucuucuc auaggaaugc uagaggaaac agaacacugc 2400

cuuacaguca ccucauguug cagaccaugu uuaugguaau acacacuuuc caaaaugagc 2460

cuuaaaaauu guaaagggga uacuauaaau gugcuaaguu auuugagacu uccucaguuu 2520

aaaaaguggg uuuuaaaucu ucugucuccc uguuuuucua aucaaggggu uaggacuuug 2580

cuaucucuga gaugucugcu acuugcugca aauucugcag cugucugcug cucuaaagag 2640

uacagugcac uagagggaag uguucccuuu aaaaauaaga acaacugucc uggcuggaga 2700

aucucacaag cggaccagag aucuuuuuaa aucccugcua cugucccuuc ucacaggcau 2760

ucacagaacc cuucugauuc guaaggguua cgaaacucau guucuucucc agucccccugu 2820

gguuucuguu ggagcauaag guuuccagua agcgggaggg cagauccaac ucagaaccau 2880

[0081]

gcagauaagg agccucuggc aaaugggugc ucaucagaac gcguggauuc ucuuucaugg 2940

cagaaugcuc uuggacucgg uucuccaggc cugauucccc gacuccaucc uuuuucaggg 3000

guuauuuaaa aaucugccuu agauucuaua gugaagacaa gcauuucaag aaagaguuac 3060

cuggaucagc caugcucagc ugugacgccu gaauaacugu cuacuuuauc uucacugaac 3120

cacucacucu guguaaaggc caacagauuu uuaauguggu uuucauauca aaagaucaug 3180

uugggauuaa cuugccuuuu uccccaaaaa auaaacucuc aggcaagcau uucuuuaaag 3240

cuauuaaggg aguauauacu ugaguacuua uugaaaugga caguaauaag caaauguucu 3300

uauaaugcua ccugauuucu augaaaugug uuugacaagc caaaauucua ggauguagaa 3360

aucuggaaag uucauuuccu gggauucacu ucuccaggga uuuuuuaaag uuaauuuggg 3420

aaauuaacag caguucacuu uauugugagu cuuugccaca uuugacugaa uugagcuguc 3480

auuuguacau uuaaagcagc uguuuugggg ucugugagag uacauguauu auauacaagc 3540

acaacagggc uugcacuaaa gaauugucau uguaauaaca cuacuuggua gccuaacuuc 3600

auauauguau ucuuaauugc acaaaaaguc aauaauuugu caccuugggg uuuugaaugu 3660

uugcuuuaag uguuggcuau uucuauguuu uauaaaccaa aacaaaauuu ccaaaaacaa 3720

ugaaggaaac caaaauaaau auuucugcau uucaggugaa aaaaaaaaaa aaaaaa 3776

<210> 48
<211> 698
<212> PRT
<213> 智人

<400> 48

Met Gln Ala His Glu Leu Phe Arg Tyr Phe Arg Met Pro Glu Leu Val
1 5 10 15

Asp Phe Arg Gln Tyr Val Arg Thr Leu Pro Thr Asn Thr Leu Met Gly
20 25 30

[0082]

Phe Gly Ala Phe Ala Ala Leu Thr Thr Phe Trp Tyr Ala Thr Arg Pro
35 40 45

Lys Pro Leu Lys Pro Pro Cys Asp Leu Ser Met Gln Ser Val Glu Val
50 55 60

Ala Gly Ser Gly Gly Ala Arg Arg Ser Ala Leu Leu Asp Ser Asp Glu
65 70 75 80

Pro Leu Val Tyr Phe Tyr Asp Asp Val Thr Thr Leu Tyr Glu Gly Phe
85 90 95

Gln Arg Gly Ile Gln Val Ser Asn Asn Gly Pro Cys Leu Gly Ser Arg
100 105 110

Lys Pro Asp Gln Pro Tyr Glu Trp Leu Ser Tyr Lys Gln Val Ala Glu
115 120 125

Leu Ser Glu Cys Ile Gly Ser Ala Leu Ile Gln Lys Gly Phe Lys Thr
130 135 140

Ala Pro Asp Gln Phe Ile Gly Ile Phe Ala Gln Asn Arg Pro Glu Trp
145 150 155 160

Val Ile Ile Glu Gln Gly Cys Phe Ala Tyr Ser Met Val Ile Val Pro
165 170 175

Leu Tyr Asp Thr Leu Gly Asn Glu Ala Ile Thr Tyr Ile Val Asn Lys
180 185 190

Ala Glu Leu Ser Leu Val Phe Val Asp Lys Pro Glu Lys Ala Lys Leu
195 200 205

Leu Leu Glu Gly Val Glu Asn Lys Leu Ile Pro Gly Leu Lys Ile Ile
210 215 220

Val Val Met Asp Ala Tyr Gly Ser Glu Leu Val Glu Arg Gly Gln Arg
225 230 235 240

Cys Gly Val Glu Val Thr Ser Met Lys Ala Met Glu Asp Leu Gly Arg
245 250 255

Ala Asn Arg Arg Lys Pro Lys Pro Pro Ala Pro Glu Asp Leu Ala Val
260 265 270

[0083] Ile Cys Phe Thr Ser Gly Thr Thr Gly Asn Pro Lys Gly Ala Met Val
275 280 285

Thr His Arg Asn Ile Val Ser Asp Cys Ser Ala Phe Val Lys Ala Thr
290 295 300

Glu Asn Thr Val Asn Pro Cys Pro Asp Asp Thr Leu Ile Ser Phe Leu
305 310 315 320

Pro Leu Ala His Met Phe Glu Arg Val Val Glu Cys Val Met Leu Cys
325 330 335

His Gly Ala Lys Ile Gly Phe Phe Gln Gly Asp Ile Arg Leu Leu Met
340 345 350

Asp Asp Leu Lys Val Leu Gln Pro Thr Val Phe Pro Val Val Pro Arg
355 360 365

Leu Leu Asn Arg Met Phe Asp Arg Ile Phe Gly Gln Ala Asn Thr Thr
370 375 380

Leu Lys Arg Trp Leu Leu Asp Phe Ala Ser Lys Arg Lys Glu Ala Glu

385 390 395 400

Leu Arg Ser Gly Ile Ile Arg Asn Asn Ser Leu Trp Asp Arg Leu Ile
405 410 415

Phe His Lys Val Gln Ser Ser Leu Gly Gly Arg Val Arg Leu Met Val
420 425 430

Thr Gly Ala Ala Pro Val Ser Ala Thr Val Leu Thr Phe Leu Arg Ala
435 440 445

Ala Leu Gly Cys Gln Phe Tyr Glu Gly Tyr Gly Gln Thr Glu Cys Thr
450 455 460

Ala Gly Cys Cys Leu Thr Met Pro Gly Asp Trp Thr Ala Gly His Val
465 470 475 480

Gly Ala Pro Met Pro Cys Asn Leu Ile Lys Leu Val Asp Val Glu Glu
485 490 495

Met Asn Tyr Met Ala Ala Glu Gly Glu Gly Glu Val Cys Val Lys Gly
[0084] 500 505 510

Pro Asn Val Phe Gln Gly Tyr Leu Lys Asp Pro Ala Lys Thr Ala Glu
515 520 525

Ala Leu Asp Lys Asp Gly Trp Leu His Thr Gly Asp Ile Gly Lys Trp
530 535 540

Leu Pro Asn Gly Thr Leu Lys Ile Ile Asp Arg Lys Lys His Ile Phe
545 550 555 560

Lys Leu Ala Gln Gly Glu Tyr Ile Ala Pro Glu Lys Ile Glu Asn Ile
565 570 575

Tyr Met Arg Ser Glu Pro Val Ala Gln Val Phe Val His Gly Glu Ser
580 585 590

Leu Gln Ala Phe Leu Ile Ala Ile Val Val Pro Asp Val Glu Thr Leu
595 600 605

Cys Ser Trp Ala Gln Lys Arg Gly Phe Glu Gly Ser Phe Glu Glu Leu
610 615 620

Cys Arg Asn Lys Asp Val Lys Lys Ala Ile Leu Glu Asp Met Val Arg
625 630 635 640

Leu Gly Lys Asp Ser Gly Leu Lys Pro Phe Glu Gln Val Lys Gly Ile
645 650 655

[0085]

Thr Leu His Pro Glu Leu Phe Ser Ile Asp Asn Gly Leu Leu Thr Pro
660 665 670

Thr Met Lys Ala Lys Arg Pro Glu Leu Arg Asn Tyr Phe Arg Ser Gln
675 680 685

Ile Asp Asp Leu Tyr Ser Thr Ile Lys Val
690 695

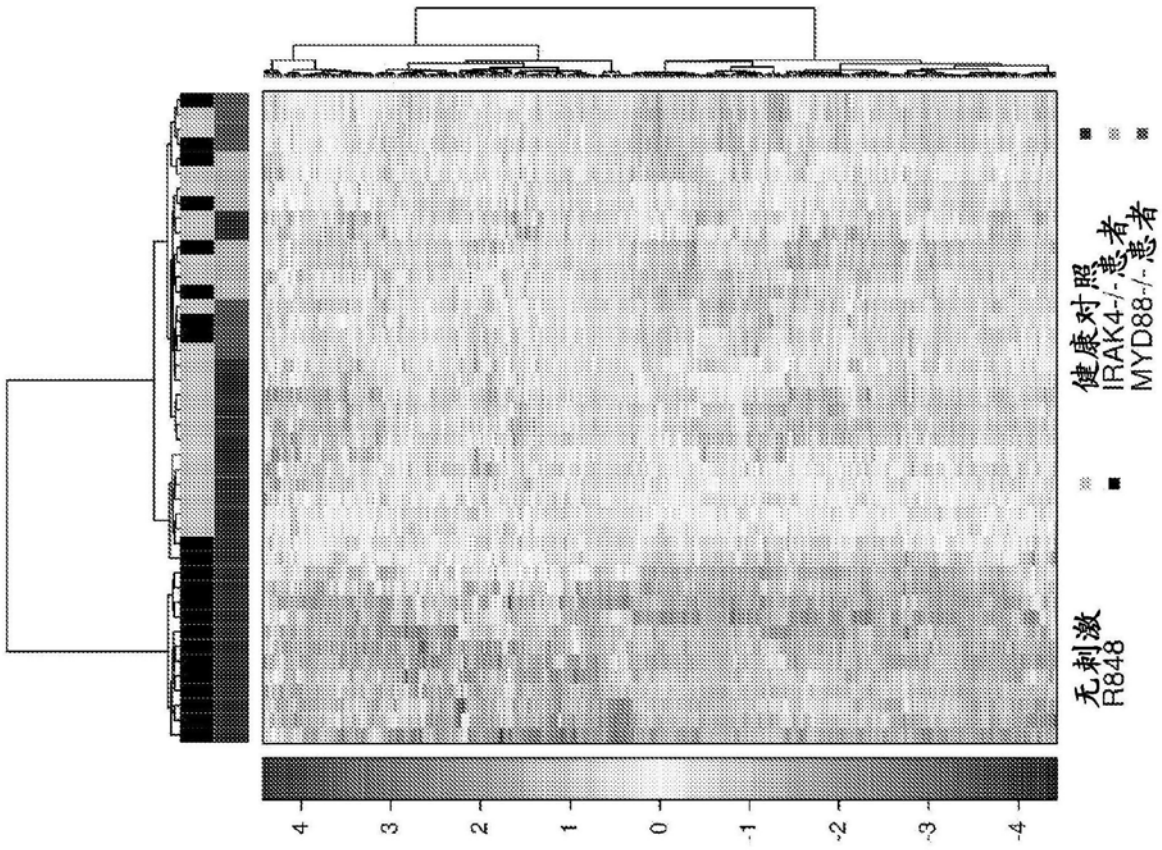


图1A

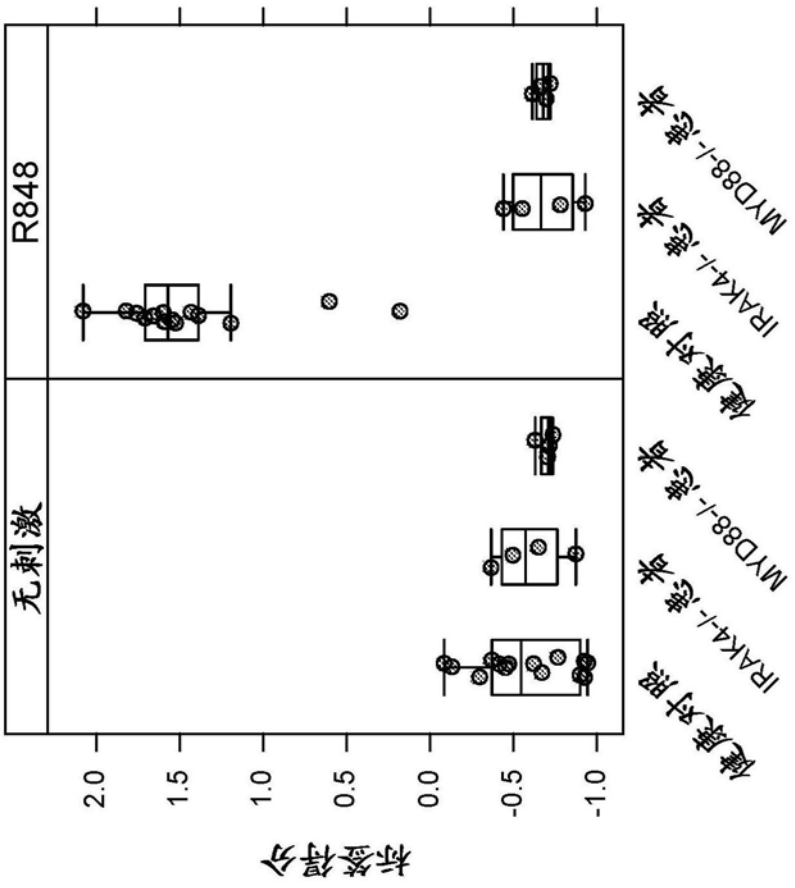

R848
无刺激
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
标签得分
磷脂对照
IRAK4-/- 骨髓
MYD88-/- 骨髓
磷脂对照
IRAK4-/- 骨髓
MYD88-/- 骨髓

图1B

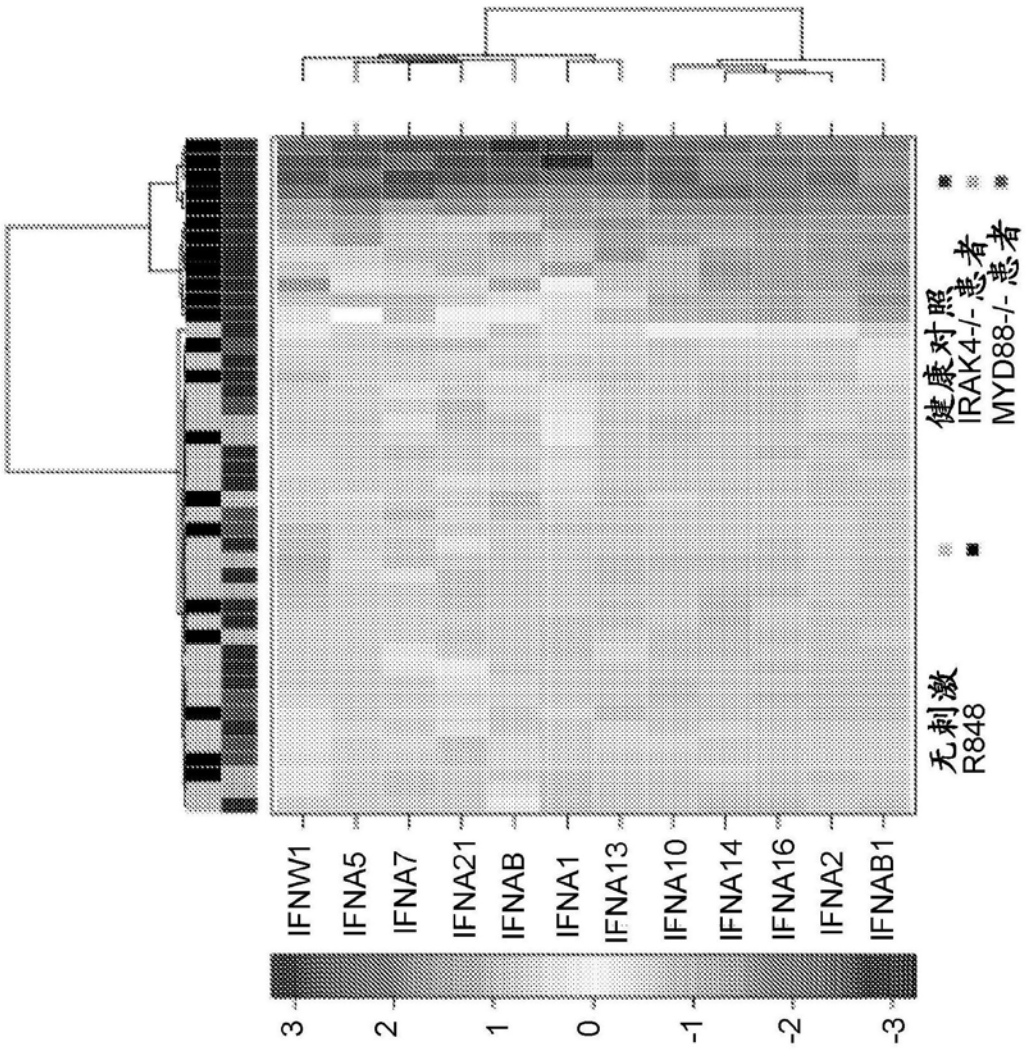

健康对照
IRAK4-/- 患者
MYD88-/- 患者
无刺激
R848
IFNW1
IFNA5
IFNA7
IFNA21
IFNAB
IFNA1
IFNA13
IFNA10
IFNA14
IFNA16
IFNA2
IFNAB1
3
2
1
0
-1
-2
-3

图2

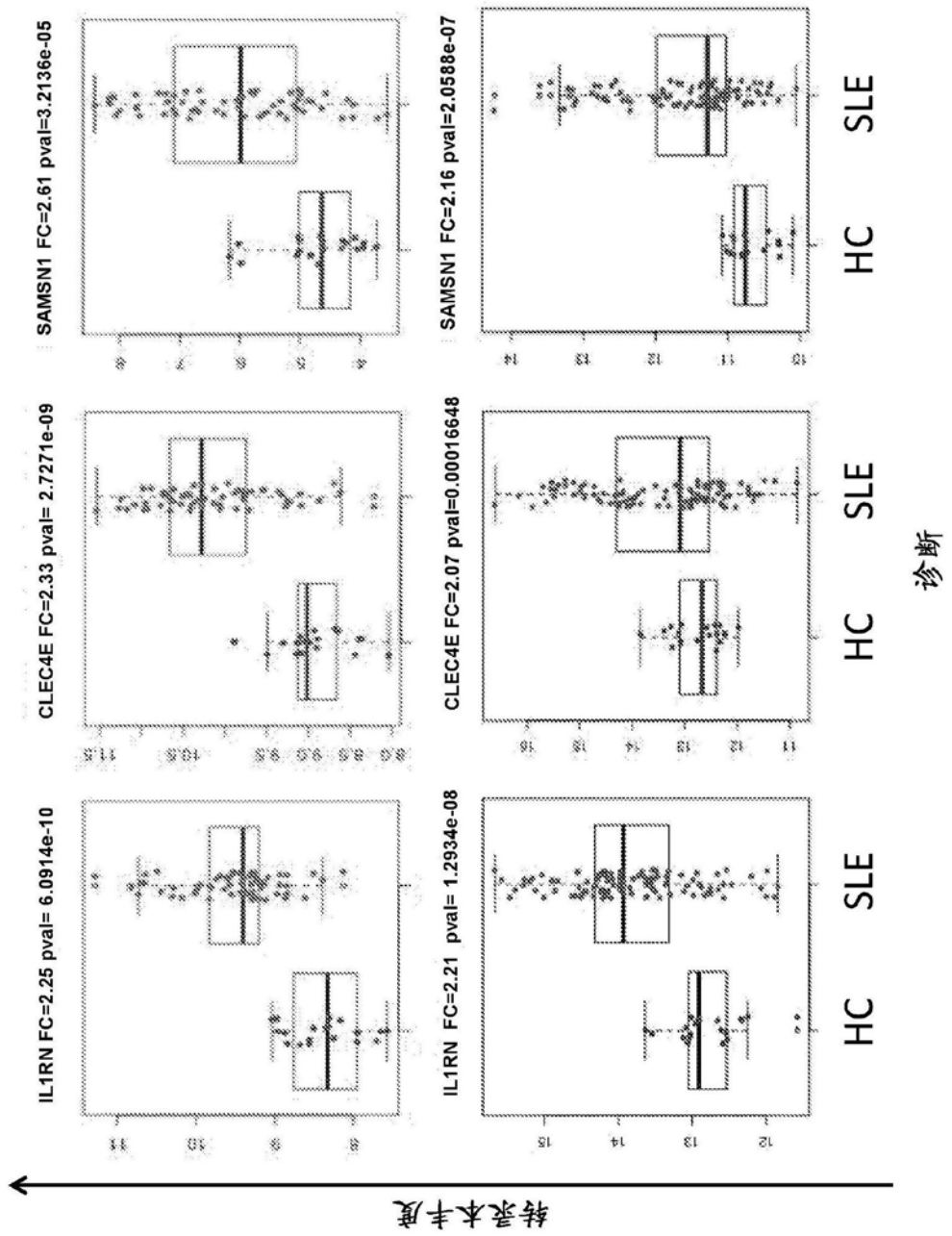

SAMSN1 FC=2.61 pval=3.2136e-05
SAMSN1 FC=2.16 pval=2.0588e-07
CLEC4E FC=2.33 pval= 2.7271e-09
CLEC4E FC=2.07 pval=0.00016648
IL1RN FC=2.25 pval= 6.0914e-10
IL1RN FC=2.21 pval= 1.2934e-08
HC
SLE
HC
SLE
HC
SLE
HC
SLE
诊断
转录本丰度
密歇根
(微阵列SPR134;
SLE n=61; HC= 20)
ROSE
(RNAseq NGS 327;
SLE n=103; 健康= 19)

图3

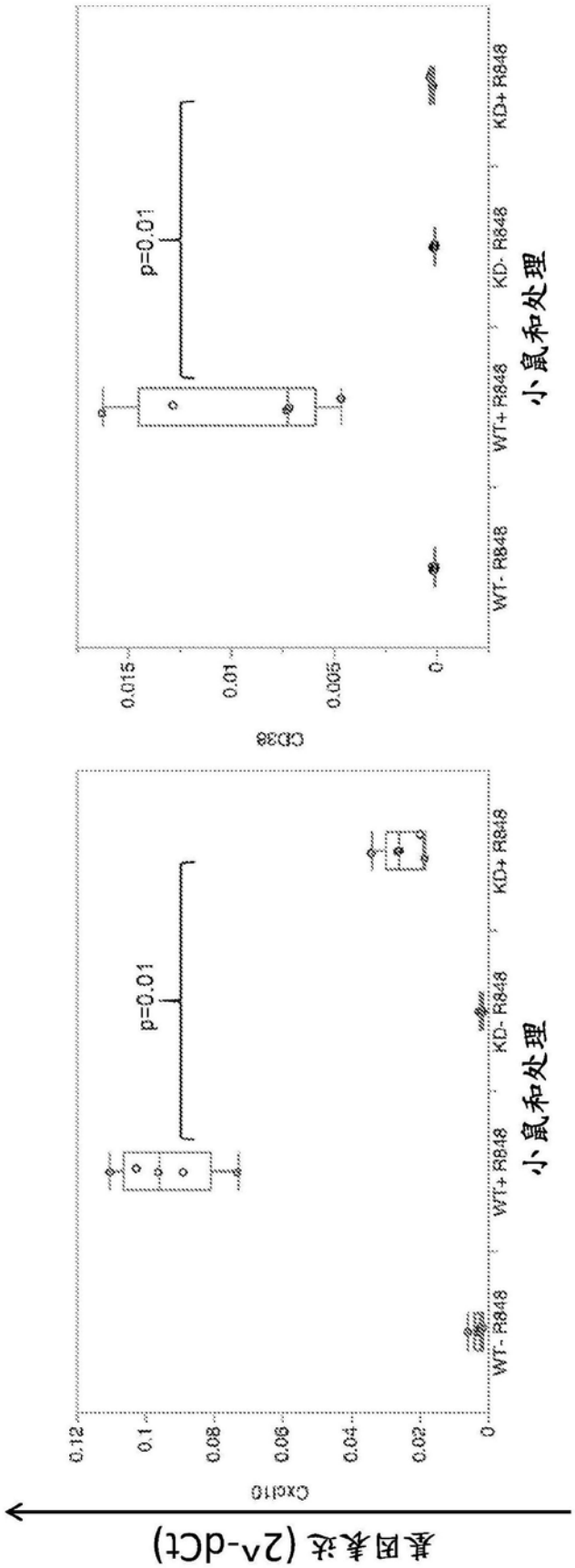

基因表达 (2^-dCt)
Cxcl10
0.12
0.1
0.08
0.06
0.04
0.02
0
p=0.01
WT- R848
WT+ R848
KD- R848
KD+ R848
小鼠和处理
CD38
0.015
0.01
0.005
0
p=0.01
WT- R848
WT+ R848
KD- R848
KD+ R848
小鼠和处理

图4

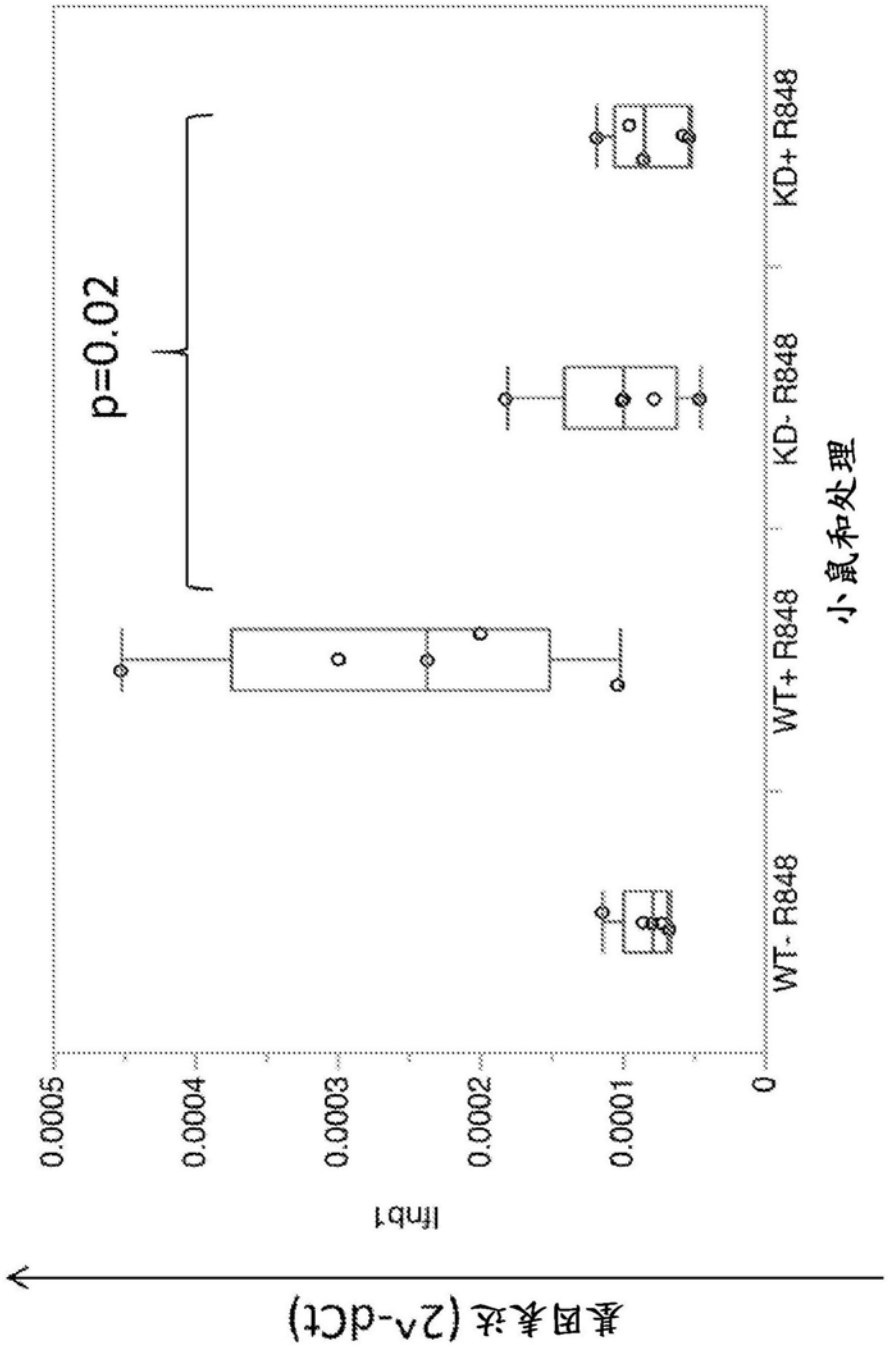

基因表达(2^-dCt)
Ifnb1
0.0005
0.0004
0.0003
0.0002
0.0001
0
p=0.02
WT- R848
WT+ R848
KD- R848
KD+ R848
小鼠和处理

图5

基因	人 IRAK4-/- WB 中 R848 诱导的受损 HC 相对于 IRAK4 缺陷中的倍数变化 (log2) 差异	p 值	IRAK4 KD 小鼠巨噬细胞中 R848 诱导的受损 KD 相对于 WT 中的基因表达比率	SLE 全血中的增加 倍数变化 (log2) (ROSE)	p 值 (ROSE)
CXCL10	-6.21	0.0001	-2.77	1.99	2.5E-09
CCL8	-5.81	0.0002	-10.87	2.66	1.4E-09
IL1RN	-4.61	0.0000	-10.13	1.17	1.9E-08
GPR84	-3.72	0.0003	-3.81	0.89	9.5E-05
C15orf48	-3.68	0.0120	-5.36	1.59	1.2E-09
SOCS3	-2.96	0.0001	-7.66	0.57	1.8E-02
DRAM1	-2.93	0.0000	-3.63	0.47	6.2E-04
CXCL11	-2.79	0.0388	-8.10	2.2	1.2E-09
GADD45B	-2.6	0.0002	-5.44	0.77	3.2E-08
TNFAIP6	-2.53	0.0101	-9.21	1.72	1.0E-10
BCL2A1	-2.48	0.0217	-4.80	1.47	1.2E-09
SOCS1	-2.31	0.0005	-7.85	1.17	5.6E-07
TNFAIP3	-2.10	0.0001	-7.03	0.43	9.3E-04
CSRNP1	-2.07	0.0001	-1.90	0.74	6.9E-05
PLSCR1	-2.04	0.0165	-1.74	1.63	1.0E-10
CLEC4E	-2.01	0.0034	-4.77	1.03	2.8E-04
PFKFB3	-2.00	0.0018	-8.06	0.47	3.9E-02
CDKN1A	-1.82	0.0459	-2.97	0.39	4.2E-02
B4GALT5	-1.79	0.0013	-2.83	0.61	9.4E-03
CD38	-1.77	0.0006	-30.12	1.27	1.2E-06
SAMSN1	-1.55	0.0393	-5.39	1.14	3.1E-07
ACSL1	-1.51	0.0246	-4.03	0.77	1.8E-03
IL15RA	-1.39	0.0001	-1.91	0.49	6.9E-05
AQP9	-1.29	0.0060	-3.20	0.48	3.9E-02

图6

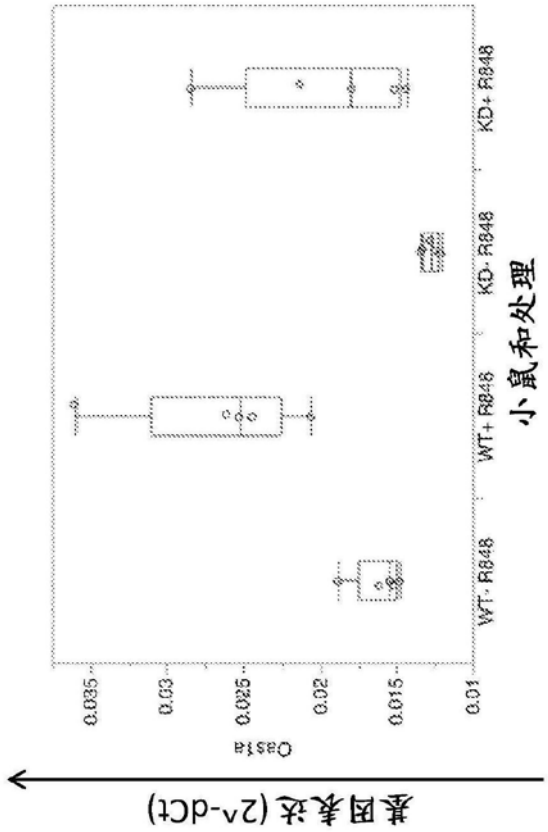

基因表达(2^-dCt)
Cas13a
0.035
0.03
0.025
0.02
0.015
0.01
WT- R848
WT+ R848
KD- R848
KD+ R848
小鼠和处理

图7A

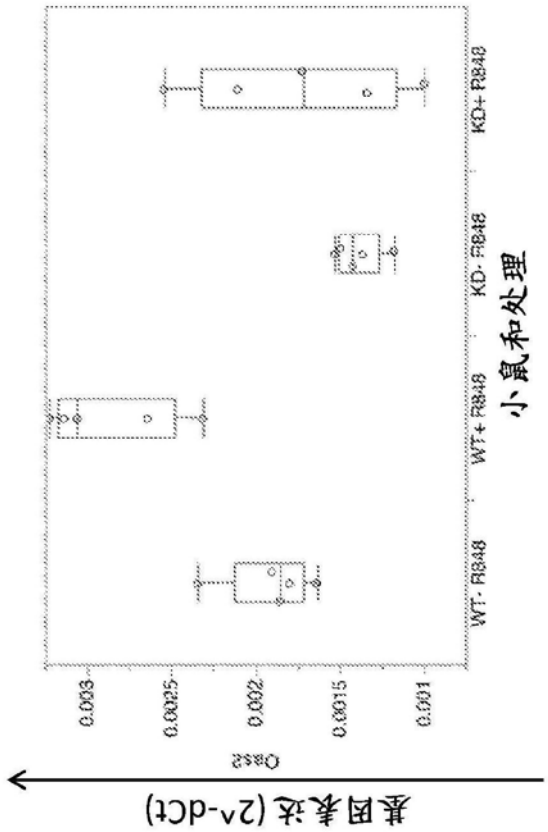

基因表达(2^-dCt)
0.003
0.0025
0.002
0.0015
0.001
Data
WT- R848
WT+ R848
KD- R848
KD+ R848
小鼠和处理

图7B

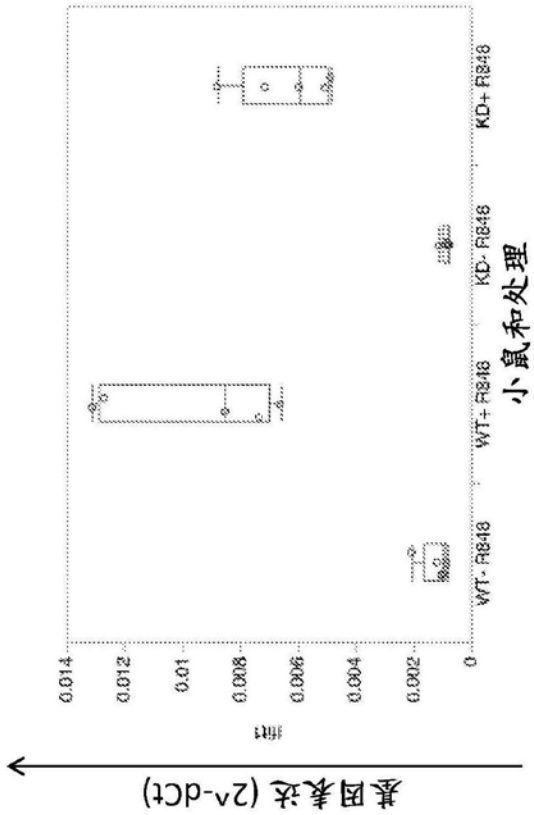

基因表达 (2^-dCt)
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
WT- R848
WT+ R848
KD- R848
KD+ R848
小鼠和处理

图7C

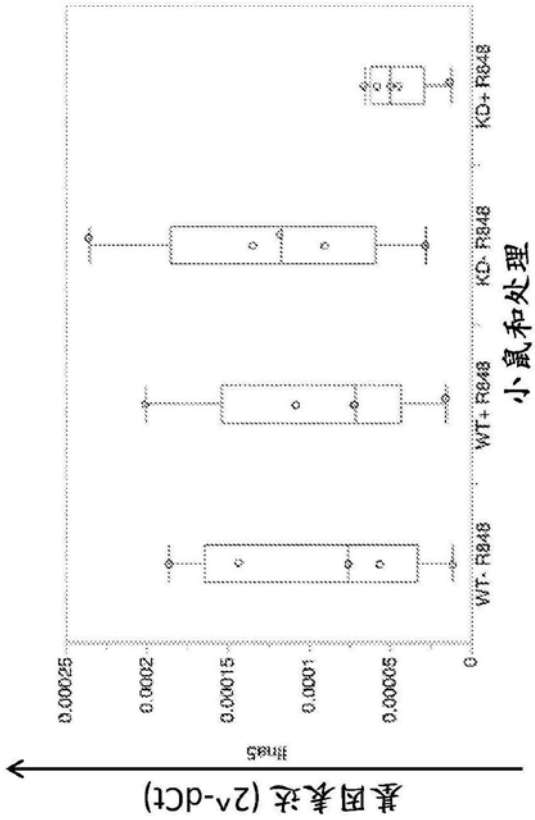

基因表达 (2^-dCt)
Ifnb1
0
0.00005
0.0001
0.00015
0.0002
0.00025
WT- R848
WT+ R848
KO- R848
KO+ R848
小鼠和处理

图7D

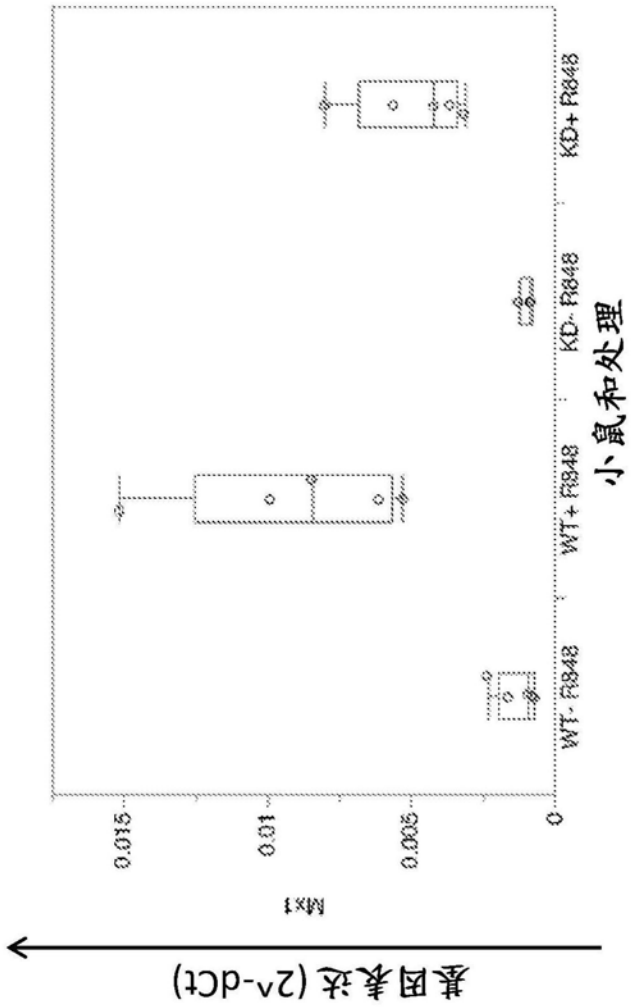
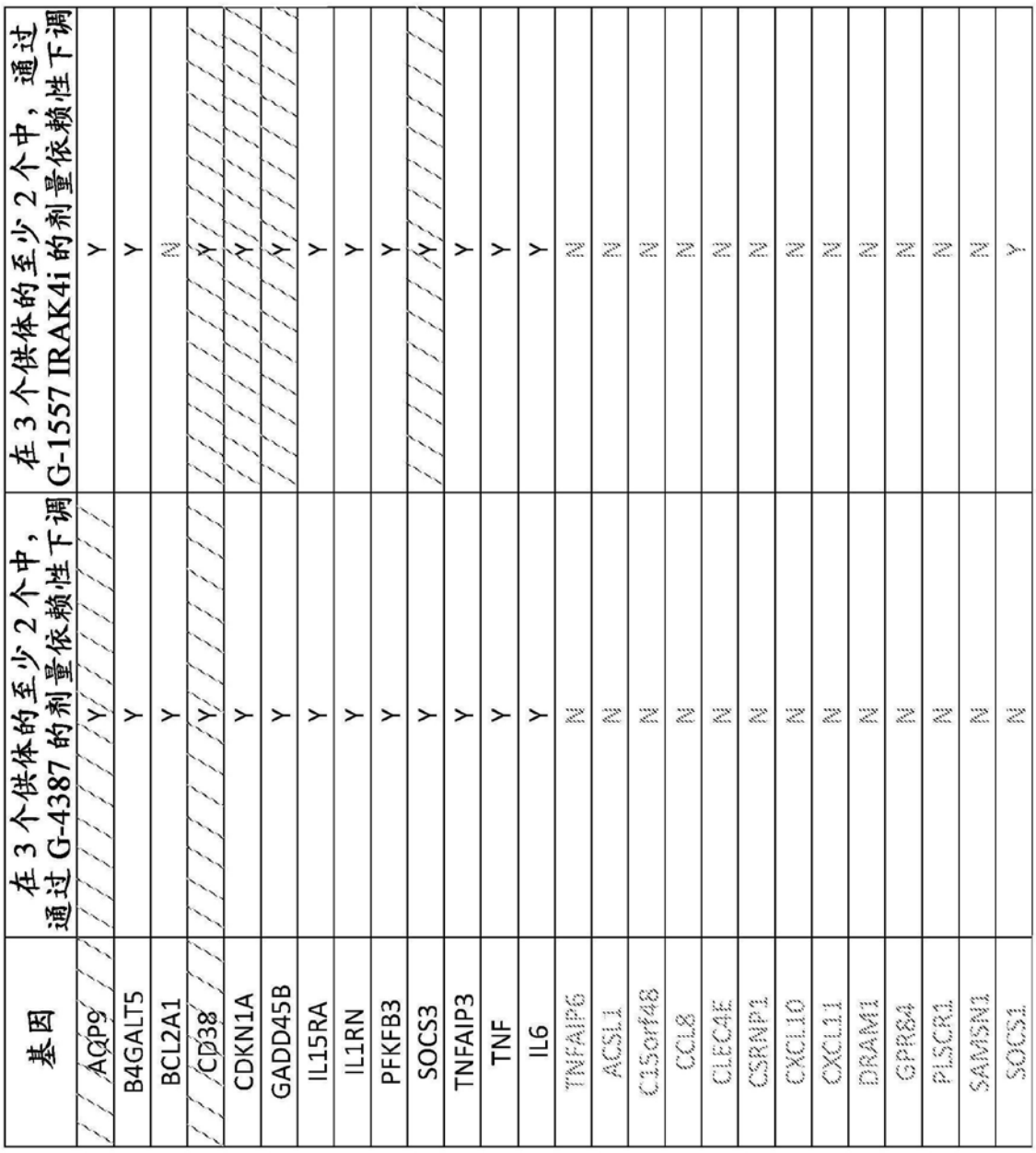

基因表达(2^-dCt)
Max
0.015
0.01
0.005
0
WT- R848
WT+ R848
KD- R848
KD+ R848
小鼠和处理

图7E



基因	在3个供体的至少2个中，通过G-4387的剂量依赖性下调	在3个供体的至少2个中，通过G-1557 IRAK4i的剂量依赖性下调
AQP9	Y	Y
B4GALT5	Y	Y
BCL2A1	Y	N
CD38	Y	Y
CDKN1A	Y	Y
GADD45B	Y	Y
IL15RA	Y	Y
IL1RN	Y	Y
PFKFB3	Y	Y
SOCS3	Y	Y
TNFAIP3	Y	Y
TNF	Y	Y
IL6	Y	Y
TNFAIP6	N	N
ACSL1	N	N
C15orf48	N	N
CCL8	N	N
CLEC4E	N	N
CSRNP1	N	N
CXCL10	N	N
CXCL11	N	N
DRAM1	N	N
GPR84	N	N
PLSCR1	N	N
SAMSN1	N	N
SOCS1	N	Y

通过相应的SMI在所有3个供体中的剂量依赖性下调

图8

基因	G-4387 IC50 (268 nM)		G-4387 IC70 (553 nM)		G-4387 IC90 (1.75 uM)		G-4387 5 uM	
	相对于对照的降低 %	p 值	相对于对照的降低 %	p 值	相对于对照的降低 %	p 值	相对于对照的降低 %	p 值
AQP9	0	1	-10.1	0.6	-31.7	0.2	-52	0.02*
B4GALT5	-9.2	0.5	-20	0.1	-27.4	0.07	-37.2	0.01*
SOCS1	-7.5	0.6	-6	0.6	-36.2	0.02*	-52.2	0.0005*
CD38	-16.9	0.1	-34.5	0.004*	-47.5	0.0008*	-47	0.0003*
CDKN1A	-7.2	0.6	-8.1	0.6	-24.8	0.2	-40.8	0.03*
GADD45B	-12.8	0.3	-18.2	0.2	-26.1	0.09	-38.6	0.008*
IL15RA	-4.8	0.8	-5.4	0.8	-18.4	0.4	-62.3	0.005*
SOCS3	-12.1	0.2	-26.2	0.004*	-56.3	<.0001*	-59.3	<.0001*
TNFAIP3	-7.9	0.5	-20.1	0.1	-35	0.02*	-50.3	0.0007*
TNF	-43.5	0.02*	-55.1	0.006*	-67.7	0.003*	-59.5	0.003*
IL6	-39.7	0.0006*	-53.2	<.0001*	-65	<.0001*	-54.2	<.0001*

基因	G-1557 IC50 (13 nM)		G-1557 IC70 (25 nM)		G-1557 IC90 (70 nM)		G-1557 200 nM	
	相对于对照的降低 %	p 值	相对于对照的降低 %	p 值	相对于对照的降低 %	p 值	相对于对照的降低 %	p 值
AQP9	-41.1	0.05	-57.8	0.007*	-62.4	0.004*	-70	0.002*
B4GALT5	-26.7	0.05	-35.3	0.01*	-32.2	0.02*	-45.8	0.002*
SOCS1	-46.9	0.002*	-57.1	0.0003*	-55	0.0004*	-66.4	<.0001*
CD38	-13.3	0.2	-28.1	0.01*	-30.1	0.01*	-42.3	0.0008*
CDKN1A	-30.2	0.08	-51.9	0.005*	-43.5	0.02*	-61.7	0.001*
GADD45B	-25.8	0.06	-39.5	0.007*	-35.8	0.01*	-49.5	0.001*
IL15RA	-27.6	0.2	-51.8	0.02*	-48.5	0.03*	-57.2	0.01*
SOCS3	-43.3	<.0001*	-61.5	<.0001*	-59.9	<.0001*	-74.9	<.0001*
TNFAIP3	-42.7	0.003*	-57.1	0.0002*	-52.5	0.0004*	-62.2	<.0001*
TNF	-28.5	0.1	-56.2	0.005*	-48.2	0.01*	-63.7	0.002*
IL6	-29	0.007*	-50.7	<.0001*	-52.4	<.0001*	-65	<.0001*

阳性对照：TNFa 和 IL6.

* 显著的 p 值

图9

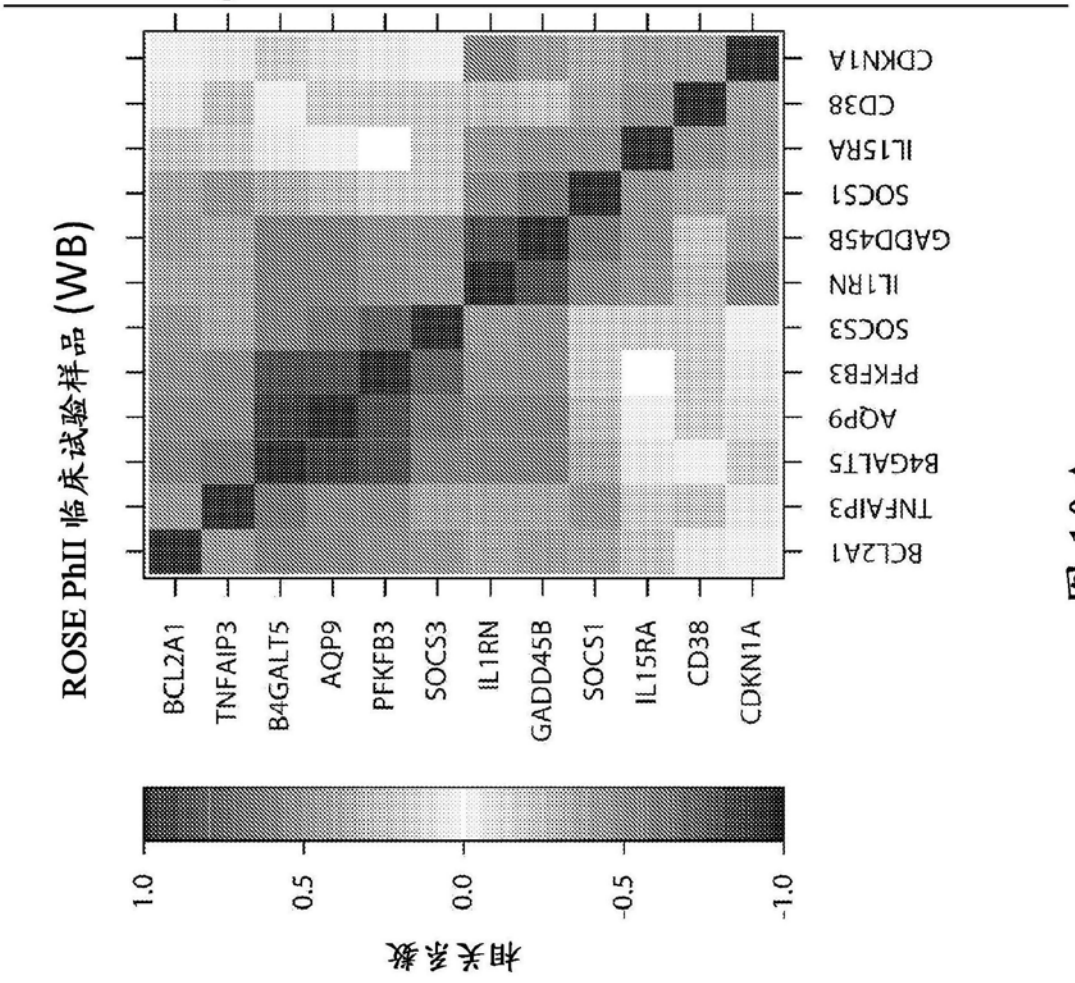

ROSE PhII 临床试验样品 (WB)
BCL2A1
TNFAIP3
B4GALT5
AQP9
PFKFB3
SOCS3
IL1RN
GADD45B
SOCS1
IL15RA
CD38
CDKN1A
1.0
0.5
0.0
-0.5
-1.0
相关系数

图 10A

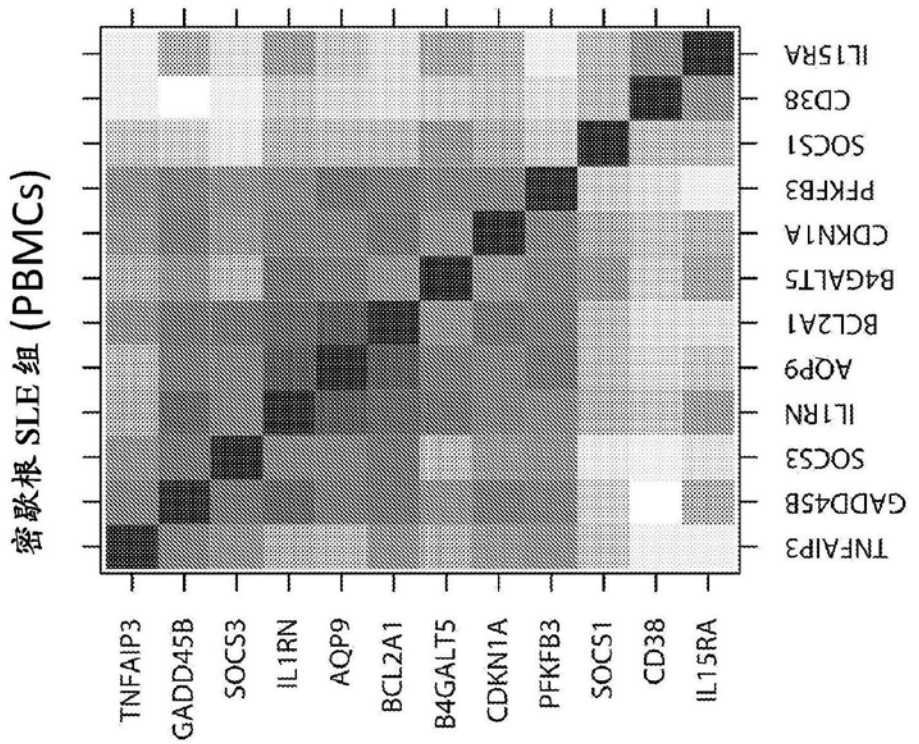

密歇根 SLE 组 (PBMCs)
TNFAIP3
GADD45B
SOCS3
IL1RN
AQP9
BCL2A1
B4GALT5
CDKN1A
PFKFB3
SOCS1
CD38
IL15RA

图 10B