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(54) Title: GENE EXPRESSION BIOMARKERS OF LAQUINIMOD RESPONSIVENESS

(57) Abstract: This invention provides a method of predicting clinical responsiveness to laquinimod therapy in a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome comprising evaluating expression of a biomarker in the subject. This invention also provides a method of treating said subject comprising determining whether the subject is a laquimmod-responder by evaluating expression of a biomarker. Also provided is laquinimod or a pharmaceutical composition comprising laquinimod for use in treating said subject, and a therapeutic package for use in dispensing to said subject, wherein the subject has been identified as a laquimmod-responder or expression of a biomarker in the subject is up-regulated or suppressed.

GENE EXPRESSION BIOMARKERS OF LAQUINIMOD RESPONSIVENESS

Throughout this application, various publications are referred to by first author and year of publication. Full citations for these publications are presented in a References section immediately before the claims. Disclosures of the publications cited in the References section in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as of the date of the invention described herein.

Background

Multiple Sclerosis (MS) is a neurological disease affecting more than 1 million people worldwide. It is the most common cause of neurological disability in young and middle-aged adults and has a major physical, psychological, social and financial impact on subjects and their families, friends and bodies responsible for health care (EMEA Guideline, 2006).

A clinically isolated syndrome (CIS) is a single monosymptomatic attack suggestive of MS, such as optic neuritis, brain stem symptoms, and partial myelitis. Patients with CIS that experience a second clinical attack are generally considered to have clinically definite multiple sclerosis (CDMS). Various MS disease stages and/or types are described in Multiple Sclerosis Therapeutics (Duntiz, 1999). Among them, relapsing-remitting multiple sclerosis (RRMS) is the most common form at the time of initial diagnosis. Many subjects with RRMS have an initial relapsing-remitting course for 5-15 years, which then advances into the secondary progressive MS (SPMS) disease course. There are currently a number of disease-modifying medications approved for use in relapsing MS (RMS), which includes RRMS and SPMS (The Disease Modifying Drug Brochure, 2006). These include interferon beta 1-a (Avonex® and Rebif®), interferon beta 1-b (Betaseron®), glatiramer acetate (Copaxone®), mitoxantrone (Novantrone®), natalizumab (Tysabri®) and Fingolimod (Gilenya®). Immunosuppressants or cytotoxic agents are used in some subjects after failure of conventional therapies. However, the relationship between changes of the immune response induced by these agents and the clinical efficacy in MS is far from settled (EMEA Guideline, 2006).

Other therapeutic approaches include symptomatic treatment which refers to all therapies applied to improve the symptoms caused by the disease (EMEA Guideline, 2006) and treatment of acute relapses with corticosteroids. While steroids do not affect the course of MS over time, they can reduce the duration and severity of attacks in some subjects.

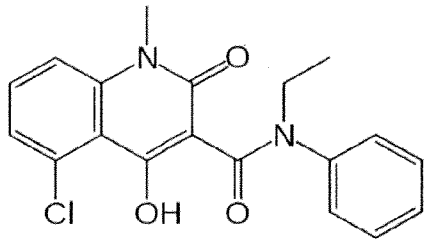
Laquinimod (LAQ)

Laquinimod (TV-5600) is a novel synthetic compound with high oral bioavailability which has been suggested as an oral formulation for the treatment of Multiple Sclerosis (MS) (Polman,

2005; Sandberg-Wollheim, 2005; Comi et al 2008). Laquinimod and its sodium salt form are described, for example, in U.S. Patent No. 6,077,851. The mechanism of action of laquinimod is not fully understood.

Animal studies show it causes a Th1 (T helper 1 cell, produces pro-inflammatory cytokines) to Th2 (T helper 2 cell, produces anti-inflammatory cytokines) shift with an anti-inflammatory profile (Yang, 2004; Brück, 2011). Another study demonstrated (mainly via the NFkB pathway) that laquinimod induced suppression of genes related to antigen presentation and corresponding inflammatory pathways (Gurevich, 2010). Other suggested potential mechanisms of action include inhibition of leukocyte migration into the CNS, increase of axonal integrity, modulation of cytokine production, and increase in levels of brain-derived neurotrophic factor (BDNF) (Runström, 2002; Brück, 2011).

Laquinimod showed a favorable safety and tolerability profile in two phase III trials (Results of Phase III BRAVO Trial Reinforce Unique Profile of Laquinimod for Multiple Sclerosis Treatment; Teva Pharma, Active Biotech Post Positive Laquinimod Phase 3 ALLEGRO Results).



IUPAC: 5-chloro-*N*-ethyl-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-1,2-dihydroquinoline-3-carboxamide

As MS therapeutic options grow, the ability to identify subjects who will respond more favorably to therapy and specifically to laquinimod has become increasingly significant.

Summary of the Invention

The subject invention provides a method of predicting clinical responsiveness to laquinimod therapy in subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, the method comprising evaluating expression of a biomarker in the subject, so as to thereby predict clinical responsiveness to laquinimod, wherein the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

The subject invention provides a method of treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome with laquinimod, comprising the steps of: a) determining whether the subject is a laquinimod responder by evaluating expression of a biomarker in the subject, and b) administering to the subject an amount of laquinimod effective to treat the subject only if the subject is identified as a laquinimod responder, so as to thereby treat the subject, wherein the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

The subject invention also provides a method for treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome comprising the steps of: a) administering to the subject a therapeutically effective amount of laquinimod, b) determining whether the subject is a laquinimod responder by evaluating expression of a biomarker in the subject; and c) administering to the subject an amount of laquinimod effective to treat the subject only if the subject is identified as a laquinimod responder, or modifying the administration of laquinimod to the subject if the subject is not identified as a laquinimod responder, so as to thereby treat the subject, wherein the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

The subject invention also provides laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein the subject has been identified as a laquinimod responder.

The subject invention also provides a pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein the subject has been identified as a laquinimod responder.

The subject invention also provides laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is up-regulated and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

The subject invention also provides a pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is up-regulated and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

The subject invention also provides laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is suppressed and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

The subject invention also provides a pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is suppressed and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

The subject invention also provides a therapeutic package for dispensing to, or for use in dispensing to, a subject identified as a laquinimod responder afflicted with multiple sclerosis or presenting a clinically isolated syndrome, which comprises: a) one or more unit doses, each such unit dose comprising an amount of laquinimod, and b) a finished pharmaceutical container therefor, said container containing said unit dose or unit doses, said container further containing or comprising labeling directing the use of said package in the treatment of said subject.

The subject invention also provides a therapeutic package for dispensing to, or for use in dispensing to, a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, which comprises: a) one or more unit doses, each such unit dose comprising an amount of laquinimod, and b) a finished pharmaceutical container therefor, said container

containing said unit dose or unit doses, said container further containing or comprising labeling directing the use of said package in the treatment of said subject, wherein expression of a biomarker in the subject is suppressed or up-regulated and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

Brief Description of the Drawings

Figure 1: Source of variation in data set (point 4) before (Figure 1A) and after (Figure 1B) normalization.

Figure 2: PCA analysis. Figure 2A- PCA analysis based on 43 genes passed FDR criteria after 6 month of treatment. Figure 2B – PCA analysis based on 1564 genes passed FDR in combined 6 and 24 months treatment data. Red dots represent patients at baseline, blue – after treatment.

Figure 3: TGFB canonical pathway. Green color represents suppressed genes from combined 6 and 24 month LAQ related gene expression signature overlaid with TGFB.

Figure 4: Immunomodulatory effects of TGFB in MS. Paradoxical effects TGFB in multiple sclerosis is shown (according to Mirshafiey et al., 2009).

Figure 5: Expression of TGFB1 in PBMCs of RRMS patients following treatment with LAQ. Protein samples (30 mg) were prepared from phenol/ethanol fractions of PBMCs derived from patients after 6 month of LAQ treatment (+) and compared to PBMCs samples of the same patients before treatment (-) (Figures 5A and 5C). From each sample 30 ug was separated on 10 % SDS-PAGE. Blots were incubated with with Rabbit a-TGFb1 (1:250) and mouse Tubulin (1:500). The signal intensities of a protein band and its surrounding background were scanned for each protein and quantified by using Quantity One 4.6.9 software (Bio-Rad Laboratories, Hercules, California). The resultant background-subtracted values of protein expression were normalized to those of Tubulin and then plotted as the relative protein levels for each patient with or without LAQ treatment (Figures 5B and 5D).

Figure 6: Expression of PAI-1 (Serpine 1) in PBMCs of patients following treatment with LAQ. Protein samples were prepared from phenol/ethanol fractions of PBMCs derived from patients after 6 month of LAQ treatment (+) and compare to PBMCs samples of the same patients before treatment (-) (A). From each sample 30 mg was separated on 10 % SDS-PAGE. Blots were incubated with Rabbit a-PAI-1 (1:500) and mouse Tubulin (1:500). The signal intensities of a protein band and its surrounding background were scanned for each protein and quantified by using Quantity One 4.6.9 software. The resultant background-subtracted values of protein expression were normalized to those of Tubulin and

then plotted as the relative protein levels for each patient with or without LAQ treatment (B).

Figure 7: Profiles of PTCRA, TGFB1 and TGFB1 related genes PF4 and CSGP5 under LAQ treatment.

Figure 8: Figure 8A and Figure 8B show proposed mechanism of LAQ effect on PBMC of RRMS patients. Figure 8C shows LAQ down-regulates leukocyte extravasation in RRMS patients. LAQ can inhibit infiltration of inflammatory cells to the CNS by direct suppression of genes associated with leukocyte extravasation or via suppression of TGFb superfamily and inflammatory cytokines.

Figure 9: Figure 9A shows LAQ treatment for six months in RRMS patients down-regulates multiple genes associated with TGFb and NFkB signaling, pro inflammatory cytokines, cell adhesion and migration. Shaded color represents down regulated genes. Figure 9B shows LAQ effects in RRMS patients after six months of treatment demonstrate down-regulation of multiple genes associated with TGFb and NFkB signaling, pro inflammatory cytokines, cell adhesion and migration. Grey color represents down regulated genes and white color depicts genes with no change in their expression level.

Figure 10: Expression of TGFb, ITGB1 and CXCR1 in RRMS patients treated with LAQ. Protein extracts were prepared from PBMCs samples derived from RRMS patients before treatment (black bars) and compared to PBMCs samples of the same patients after six months of LAQ treatment (white bars). The signal intensity of a protein bands were quantified by Quantity One 4.6.9 software. The resultant background-subtracted values of protein expression were normalized to those of Tubulin and then calculated as the relative protein levels for each patient before or after LAQ treatment. The blot images in A, B and C are representative of two out of five analyzed patients showing down regulation of TGFb, ITGB1 and CXCR1, respectively as also quantified by densitometry of bands analyzed from five patients. Data are presented as mean±SEM. Statistically significant differences are marked in graphs (n=5, paired one-tailed *t*-test).

Detailed Description of the Invention

The subject invention provides a method of predicting clinical responsiveness to laquinimod therapy in a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, the method comprising evaluating expression of a biomarker in the subject, so as to thereby predict clinical responsiveness to laquinimod, wherein the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

In one embodiment of the present invention, the method further comprises predicting positive clinical responsiveness to laquinimod if the biomarker is up-regulated in the subject. In another embodiment, the subject is naïve to laquinimod.

In another embodiment of the present invention, the method further comprises predicting positive clinical responsiveness to laquinimod if the biomarker suppressed in the subject. In another embodiment, the subject has previously received periodic laquinimod administration. In another embodiment, the expression of the biomarker is suppressed in comparison to expression of said biomarker of the patient at baseline.

In one embodiment, the subject has received periodic laquinimod administration for at least one month. In another embodiment, the subject has received periodic laquinimod administration for at least 6 months. In another embodiment, the subject has received periodic laquinimod administration for at least 12 months. In another embodiment, the subject has received periodic laquinimod administration for at least 24 months.

In one embodiment, the gene associated with inflammatory response is a gene associated with or involved in TGFb signaling, IL-12 signaling, the pathway of adhesion of phagocytes, chemotaxis of neutrophils, transmigration of leukocytes, caveolar mediated endocytosis, clathrin mediated endocytosis, and/or leukocyte extravasation signaling.

In another embodiment, the gene associated with cellular movement is a gene associated with or involved in adhesion and migration of phagocytes, chemotaxis of neutrophils, transmigration of leukocytes, invasion of cells, adhesion of cells, and/or leukocyte extravasation signaling.

In another embodiment, the gene associated with cell signaling is a gene associated with or involved in the pathway of adhesion of cells and/or neurotransmission.

In another embodiment, the gene associated with cell development is a gene associated with or involved in the pathway of G protein coupled receptor signaling, arachidonic acid metabolism and/or TGFβ signaling.

In another embodiment, the gene associated with hematological system is a gene associated with or involved in the pathway of aggregation of blood platelets, activation of blood platelets, aggregation of blood cells, coagulation of blood, intrinsic prothrombin activation pathway and/or coagulation system.

In another embodiment, the gene is TNFSF4, SELP, ITFA8, ITGB1/3/5, CXCL5/7, a BMP6 gene, ITGA2/8, ITGβ1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/1R/5/8/13/20/22R, IL-9/11/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, type II BMPR, smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1 or a combination thereof.

In one embodiment of any one of the methods, uses, pharmaceutical composition or packages described herein, the gene is ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-5/20/22, IL-9/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad2/3/4, PAI-1, SELP, ITFA8 , ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-5/13/20/22 , IL-9/11/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1, Alpha tubulin, BMP4/7, MIS, TCF2, IL5R, IL13R, IL20R, ITGB2, NKTR, TEF, CLSTN2, LUC7L2, FABP7, TPTE, FSTL1, SF3B1, LIMS1, PDE5A, XPNPEP1, C5orf4, SPANXB1, SPANXB2, SPANXF1, KRT20, TBC1D1, GRHL2, C5orf4, SEPT6, KIAA1199, SSX2IP, TPM1, CDC14B, USP47, MMRN1, CTNNAL1, SMOX, ALOX12, GLRA3, CA2, GUCY1B3, RFPL1, CLEC1B, GNG11, TSPAN32, RGS10, CALD1, PRKAR2B, CYP4F11, CLCA3P, CELSR3, CDC14B, TPM1, SEPT6, PRKG1, MAX, CCDC93, ARMCX6, LOC653354, TUBB2B, HIST1H2AJ, MFAP3L, LIMS1, GNB5, GPRASP1, SRRT, C1orf116, FBXO7, PPM1A, GUCY1B3,CTDSPL, GNAS, IGF2BP3, TPM1, HIST1H2BK, DLG4, WDR48, CALD1, LOC157627, GNB5, ZNF415,ASAP2, PSD3, GNAS,POPDC3, NRGN, ABLIM3, XYLT1, PTGIS, ARHGEF10, PDGFA,PGRMC1, HIST1H2AC, GNAS, CLDN5, MFAP3L, PGRMC1, MYST3, CAPRIN1, CALD1, FBXW7, DNM3, CD84, PRPF4B, RBM25, WASF3, GRAP2, SPARC, TAL1, NENF, XK, GP1BA,HLA-E, CA5A, LYVE1,MARCH6, NAT8B, TRIM58, RET, SDPR, TBXA2R, TMED10, APBA2, MYL9, POU1F1, H2BFS, HIST1H2BK, FAM12B, VCL, GSPT1, ALDOB, LOC150776, SMPD4, SLC37A1, SPARC, GNAS, TAS2R4, CALM3, POM121, POM121C, GRIK2, GREM1, TNNC2, EPS15L2, ENDOD1, RGS6, SF3B1, TMSB15A, ZBTB20, FUT9, ATP9A,MAX, HIST1H2AI, BAT2D1, ABL1, SNCA, GFI1B,

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MYH11, NES, SLC17A1, RBM15B, CSH1, HTR5A, CYP3A7, HTR2A, KCNV2, TOX3, CLOCK, MAGEA6, FAM12A, COL4A3, S1PR2, NAT8, ACE2, SLC22A6, SLC13A2, MYH4, APBB2, RAP1GAP, SHOX2, SLCO1A2, ETV1, MAGEA12, PLA2G6, ADRA1A, SYT5, GPR161, SEMA3F, CYP3A43, HOMER2, KCNJ5, PPL, COL17A1, CSHL1, C9orf116, PARK2, UGT2B15, CDK6, FAM174B, CELA2A, CELA2B, SPDEF, EPB41, GAB1, SMR3A, PDE6G, COL5A1, ABCA6, DMD, CYLC2, CIDEA, RAG2, HIST1H2BN, FMO6P, MAOA, ANKRD53, HAPLN1, MT1M, EHD2, GAD2, CRISP2, CSN2, SULT1C2, PCDHGA3, SSX3, FGFR2, GPR161, ATN1, CHD5, A4GALT, MYBPH, CSHL1, NCAPH2, CAPN9, CNGB1, BCAM, DRD5, NR5A2, TEF, ELAVL2, DGKB, HTR7P, RHAG, GH2, COL4A6, BMP7, SOSTDC1, SOX14, TAS2R9, LPHN2, MAP1A, OSGIN2, SLC10A2, FAM13C, EMX1, FLJ40330, CHI3L1, CDH16, SPRR1A, LOX, CALCB, GABBR2, CPB2, RASL11B, CCDC81, RUNX1, CPA1, CLCNKA, CLCNKB, FHL5, THSD7A, TFAP2C, SPAG11B, CAP2, PODNL1, SSX4, SSX4B, G6PC, RPE65, TMEM222, KDR, CHP2, GPR64, TPM2, TCEB3B, E2F5, IL5RA, AOC3, ABCF3, CPN2, ACE, NRP2, INPP5J, SMAD9, FAM155A, GART, PIR, ZNF467, ITSN2, NR1D1, THRA, RP11-35N6.1, LAMB1, EPHB3, PLA2R1, RAPGEF4, DNAJC8, ARSJ, TRIM49, GC, CDH2, ATXN3L, BTF3L1, BICC1, FAM186A, PTPRF, TRPC4, TCL6, CYP4A22, FUT6, MUC1, DKFZP434B2016, LOC643313, LDHA, LOC100131613, TRIM3, MLLT10, DZIP1, ANKRD34C, BUB1, CSPG5, FBLN1, GAD2, CLDN1, CHRNA3, SCN11A, TEX11, IL20RA, AKAP5, KBTBD10, MSTN, TLL2, NACAD, UNC93A, PTGER1, OLAH, NHLH2, SERPINA6, KRT17, KCNMA1, PRKCA, STS, LAMA1, GPR88, ACTN2, TREH, AKAP4, DKK4, PRICKLE3, IRS4, TRPV4, PCDH11Y, APBB2, SLCO2A1, DRD2, MTMR7, ZNF471, TF, NRIP2, ST6GALNAC5, COMT, PAH, LRRC19, PRKAR1B, HPR, PRDM5, NCRNA00120, LOC79999, ITSN2, CACNB2, GPR98, PREX2, FAM182B, LAMA4, ARVCF, HAS2, YOD1, PPP2R3A, COL4A1, RBM12B, GSTA3, FAM66D, OR10H2, PTHLH, ZNF674, KRT19, ACCN2, COL6A1, LOC100288442, LOC100289169, LOC728888, LOC729602, NPIPL2, NPIPL3, PDXDC2, SLC37A1, ATP6V1B1, ABI3BP, HR44, ZNF324B, ZNF584, HOXD13, ADH6, IFNA8, MYOZ2, NFATC4, ADAMTS7, FOXL1, GPR17, SLC18A3, MYH6, BOK, FGA, TEAD4, GRM1, EDNRA, C8orf79, METTL7A, FOLH1, RAD54L, SOX11, CNOT3, NTS, MAPK12, DOCK6, DNAJC6, HS3ST3A1, LOC728395, TSPY1, TSPY3, PTH, LAMB4, ALDOB, FLG, MLANA, UBE2D4, LOC100287483, KRT20, POU1F1, SLCO1B3, CLTA, MECOM, C8orf71, SULT2A1, C6orf10, SLC27A6, PRKD1, SYNPO2L, THPO, GABRR1, CFTR, PPP2R3A, DCBLD2, ANP32A, ANP32C, ANP32D, LOC723972, XYLT1, STAB1, STAB1, SASH1, PID1, FUCA1, SASH1, LRRN3, LRRN3 or a combination thereof.

In another embodiment, the gene is ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-5/20/22, IL-9/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad2/3/4, PAI-1, SELP, ITFA8 , ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-5/13/20/22 , IL-9/11/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1 or a combination thereof. In another embodiment, the gene is SELP, ITFA8 , ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/1R/5/8/13/20/22, IL-9/11/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, Smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1 or a combination thereof.

In one embodiment of any one of the methods, uses, pharmaceutical composition or packages described herein, the gene is TNFSF4, ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/5/8/20/22, IL-9/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, Smad2/3/4, PAI-1, TNFSF4, SELP, ITFA8, ITGB1/3/5, CXCL5/7, a BMP6 gene, ITGA2/8, ITGβ1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/1R/5/8/13/20/22R, IL-9/11/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, type II BMPR, smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1, IL8R (CXCR1/2), Alpha tubulin, BMP2/4/7, MIS, TCF2, LFA-1, VLA-4, IL5R, IL13R, IL20R, ITGB2, IFN gamma, TNF alpha, NKTR, TEF, CLSTN2, LUC7L2, FABP7, TPTE, FSTL1, SF3B1, LIMS1, PDE5A, XPNPEP1, C5orf4, SPANXB1, SPANXB2, SPANXF1, KRT20, TBC1D1, GRHL2, C5orf4, SEPT6, KIAA1199, SSX2IP, TPM1, CDC14B, USP47, MMRN1, CTNNAL1, SMOX, ALOX12, GLRA3, CA2, GUCY1B3, RFPL1, CLEC1B, GNG11, TSPAN32, RGS10, CALD1, PRKAR2B, CYP4F11, CLCA3P, CELSR3, CDC14B, TPM1, SEPT6, PRKG1, MAX, CCDC93, ARMCX6, LOC653354, TUBB2B, HIST1H2AJ, MFAP3L, LIMS1, GNB5, GPRASP1, SRRT, C1orf116, FBXO7, PPM1A, GUCY1B3,CTDSPL, GNAS, IGF2BP3, TPM1, HIST1H2BK, DLG4, WDR48, CALD1, LOC157627, GNB5, ZNF415,ASAP2, PSD3, GNAS,POPDC3, NRGN, ABLIM3, XYLT1, PTGIS, ARHGEF10, PDGFA,PGRMC1, HIST1H2AC, GNAS, CLDN5, MFAP3L, PGRMC1, MYST3, CAPRIN1, CALD1, FBXW7, DNM3, CD84, PRPF4B, RBM25, WASF3, GRAP2, SPARC, TAL1, NENF, XK, GP1BA,HLA-E, CA5A, LYVE1,MARCH6, NAT8B, TRIM58, RET, SDPR, TBXA2R, TMED10, APBA2, MYL9, POU1F1, H2BFS, HIST1H2BK, FAM12B, VCL, GSPT1, ALDOB, LOC150776, SMPD4, SLC37A1, SPARC, GNAS, TAS2R4, CALM3, POM121, POM121C, GRIK2, GREM1, TNNC2, EPS15L2, ENDOD1, RGS6, SF3B1, TMSB15A, ZBTB20, FUT9, ATP9A,MAX, HIST1H2AI, BAT2D1, ABL1, SNCA, GFI1B, CTSA, SNX13, RPA1, FLNA, XPNPEP1, KIF2A, ZBTB33,PSMD11,

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DCHS2, OBP2A, OBP2B, ANGPTL3, MYH11, NES, SLC17A1, RBM15B, CSH1, HTR5A, CYP3A7, HTR2A, KCNV2, TOX3, CLOCK, MAGEA6, FAM12A, COL4A3, S1PR2, NAT8, ACE2, SLC22A6, SLC13A2, MYH4, APBB2, RAP1GAP, SHOX2, SLCO1A2, ETV1, MAGEA12, PLA2G6, ADRA1A, SYT5, GPR161, SEMA3F, CYP3A43, HOMER2, KCNJ5, PPL, COL17A1, CSHL1, C9orf116, PARK2, UGT2B15, CDK6, FAM174B, CELA2A, CELA2B, SPDEF, EPB41, GAB1, SMR3A, PDE6G, COL5A1, ABCA6, DMD, CYLC2, CIDEA, RAG2, HIST1H2BN, FMO6P, MAOA, ANKRD53, HAPLN1, MT1M, EHD2, GAD2, CRISP2, CSN2, SULT1C2, PCDHGA3, SSX3, FGFR2, GPR161, ATN1, CHD5, A4GALT, MYBPH, CSHL1, NCAPH2, CAPN9, CNGB1, BCAM, DRD5, NR5A2, TEF, ELAVL2, DGKB, HTR7P, RHAG, GH2, COL4A6, BMP7, SOSTDC1, SOX14, TAS2R9, LPHN2, MAP1A, OSGIN2, SLC10A2, FAM13C, EMX1, FLJ40330, CHI3L1, CDH16, SPRR1A, LOX, CALCB, GABBR2, CPB2, RASL11B, CCDC81, RUNX1, CPA1, CLCNKA, CLCNKB, FHL5, THSD7A, TFAP2C, SPAG11B, CAP2, PODNL1, SSX4, SSX4B, G6PC, RPE65, TMEM222, KDR, CHP2, GPR64, TPM2, TCEB3B, E2F5, IL5RA, AOC3, ABCF3, CPN2, ACE, NRP2, INPP5J, SMAD9, FAM155A, GART, PIR, ZNF467, ITSN2, NR1D1, THRA, RP11-35N6.1, LAMB1, EPHB3, PLA2R1, RAPGEF4, DNAJC8, ARSJ, TRIM49, GC, IL12B, CDH2, ATXN3L, BTF3L1, BICC1, FAM186A, PTPRF, TRPC4, TCL6, CYP4A22, FUT6, MUC1, DKFZP434B2016, LOC643313, LDHA, LOC100131613, TRIM3, MLLT10, DZIP1, ANKRD34C, BUB1, CSPG5, FBLN1, GAD2, CLDN1, CHRNA3, SCN11A, TEX11, IL20RA, AKAP5, KBTBD10, MSTN, TLL2, NACAD, UNC93A, PTGER1, OLAH, NHLH2, SERPINA6, KRT17, KCNMA1, PRKCA, STS, LAMA1, GPR88, ACTN2, TREH, AKAP4, DKK4, PRICKLE3, IRS4, TRPV4, PCDH11Y, APBB2, SLCO2A1, DRD2, MTMR7, ZNF471, TF, NRIP2, ST6GALNAC5, COMT, PAH, LRRC19, PRKAR1B, HPR, PRDM5, NCRNA00120, LOC79999, ITSN2, CACNB2, GPR98, PREX2, FAM182B, LAMA4, ARVCF, HAS2, YOD1, PPP2R3A, COL4A1, RBM12B, GSTA3, FAM66D, OR10H2, PTHLH, ZNF674, KRT19, ACCN2, COL6A1, LOC100288442, LOC100289169, LOC728888, LOC729602, NPIPL2, NPIPL3, PDXDC2, SLC37A1, ATP6V1B1, PTN, ABI3BP, HR44, ZNF324B, ZNF584, HOXD13, ADH6, IFNA8, MYOZ2, NFATC4, ADAMTS7, FOXL1, GPR17, SLC18A3, MYH6, BOK, FGA, TEAD4, GRM1, EDNRA, C8orf79, METTL7A, FOLH1, RAD54L, SOX11, CNOT3, NTS, MAPK12, DOCK6, DNAJC6, HS3ST3A1, LOC728395, TSPY1, TSPY3, PTH, LAMB4, ALDOB, FLG, MLANA, UBE2D4, LOC100287483, KRT20, POU1F1, SLCO1B3, CLTA, MECOM, C8orf71, SULT2A1, C6orf10, SLC27A6, PRKD1, SYNPO2L, THPO, GABRR1, CFTR, PPP2R3A, DCBLD2, ANP32A, ANP32C, ANP32D, LOC723972, XYLT1, STAB1, STAB1, SASH1, PID1, FUCA1, SASH1, LRRN3, LRRN3 or any combination thereof.

In another embodiment, the gene is TNFSF4, ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/5/8/20/22, IL-9/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, Smad2/3/4, PAI-1, TNFSF4, SELP, ITFA8, ITGB1/3/5, CXCL5/7, a BMP6 gene, ITGA2/8, ITGβ1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/1R/5/8/13/20/22R, IL-9/11/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, type II BMPR, smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1 or any combination thereof. In yet another embodiment, the gene is TNFSF4 , ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/5/8/20/22, IL-9/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, Smad2/3/4, PAI-1 or any combination thereof.

The subject invention also provides a method of treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome with laquinimod, comprising the steps of: a) determining whether the subject is a laquinimod responder by evaluating expression of a biomarker in the subject, and b) administering to the subject an amount of laquinimod effective to treat the subject only if the subject is identified as a laquinimod responder, so as to thereby treat the subject, wherein the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

The subject invention also provides a method for treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome comprising the steps of: a) administering to the subject a therapeutically effective amount of laquinimod, b) determining whether the subject is a laquinimod responder by evaluating expression of a biomarker in the subject; and c) administering to the subject an amount of laquinimod effective to treat the subject only if the subject is identified as a laquinimod responder, or modifying the administration of laquinimod to the subject if the subject is not identified as a laquinimod responder, so as to thereby treat the subject, wherein the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

In one embodiment, the subject is identified as a laquinimod responder if the biomarker is up-regulated in the subject. In another embodiment, the subject is identified as a laquinimod responder if the biomarker is suppressed in the subject.

In one embodiment, the gene associated with inflammatory response is a gene associated with or involved in TGFb signaling, IL-12 signaling, the pathway of adhesion of phagocytes,

chemotaxis of neutrophils, transmigration of leukocytes, caveolar mediated endocytosis, clathrin mediated endocytosis, and/or leukocyte extravasation signaling.

In another embodiment, the gene associated with cellular movement is a gene associated with or involved in adhesion and migration of phagocytes, chemotaxis of neutrophils, transmigration of leukocytes, invasion of cells, adhesion of cells, and/or leukocyte extravasation signaling.

In another embodiment, the gene associated with cell signaling is a gene associated with or involved in the pathway of adhesion of cells and/or neurotransmission.

In another embodiment, the gene associated with cell development is a gene associated with or involved in the pathway of G protein coupled receptor signaling, arachidonic acid metabolism and/or TGFβ signaling.

In another embodiment, the gene associated with hematological system is a gene associated with or involved in the pathway of aggregation of blood platelets, activation of blood platelets, aggregation of blood cells, coagulation of blood, intrinsic prothrombin activation pathway and/or coagulation system.

In another embodiment, the gene is TNFSF4, SELP, ITFA8, ITGB1/3/5, CXCL5/7, a BMP6 gene, ITGA2/8, ITGβ1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/1R/5/8/13/20/22R, IL-9/11/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, type II BMPR, smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1 or a combination thereof.

In one embodiment of any one of the methods, uses, pharmaceutical composition or packages described herein, the gene is ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-5/20/22, IL-9/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad2/3/4, PAI-1, SELP, ITFA8 , ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-5/13/20/22 , IL-9/11/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1, Alpha tubulin, BMP4/7, MIS, TCF2, IL5R, IL13R, IL20R, ITGB2, NKTR, TEF, CLSTN2, LUC7L2, FABP7, TPTE, FSTL1, SF3B1, LIMS1, PDE5A, XPNPEP1, C5orf4, SPANXB1, SPANXB2, SPANXF1, KRT20, TBC1D1, GRHL2, C5orf4, SEPT6, KIAA1199, SSX2IP, TPM1, CDC14B, USP47, MMRN1, CTNNAL1, SMOX, ALOX12, GLRA3, CA2, GUCY1B3, RFPL1, CLEC1B, GNG11, TSPAN32, RGS10, CALD1, PRKAR2B, CYP4F11, CLCA3P, CELSR3, CDC14B, TPM1, SEPT6, PRKG1, MAX, CCDC93, ARMCX6, LOC653354, TUBB2B, HIST1H2AJ, MFAP3L, LIMS1, GNB5, GPRASP1, SRRT, C1orf116, FBXO7, PPM1A, GUCY1B3,CTDSPL, GNAS, IGF2BP3, TPM1, HIST1H2BK, DLG4, WDR48,

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POMP, SOX21, DNAH9, HOXC5, SERHL2, KIAA0485, ITSN1, B4GALT1, NEK2, NUPR1, CCDC93, EPO, CRABP2, TYRO3, GOLGA2, SEMA3F, BFSP2, NCAM1, FOLH1, SSX2, TMPRSS4, DCN, LPHN3, POU4F3, CEACAM5, BCL3, EXTL3, CCNA1, DDR2, PAX8, SOX5, POU3F1, PEX16, NUP62, SIGLEC11, ALDOB, GPC3, IGFALS, WDR25, FGF1, OSR2, ARID1A, GYPA, KLK13, PARVB, LILRB5, RIMS2, C19orf21, HOXD1, PRSS3, FLT1, ATP6V1C1, LOX, CRYBB3, CA12, PRKG2, MASP1, LOC728395, LOC728403, TSPY1, PDCD1, GGTLC1, AQP8, KRT16, AICDA, BRD8, C1orf95, OR3A2, PFKFB2, FRZB, PAK3, MEIS2, ZSCAN2, MYH7, VWA1, LSAMP, SRC, UGT1A1, UGT1A10, UGT1A3, UGT1A4, UGT1A5, UGT1A6, UGT1A7, UGT1A8, UGT1A9, DIO1, TADA3L, NFASC, CALCRL, NBLA00301, MAB21L1, FBXO42, COL10A1, CFB, SNX7, FOXN1, SRY, HLF, CLCA3P, DAZ1, DAZ2, DAZ3, DAZ4, GPR3, TMPRSS11E, EMID1, KCNMB2, MUC5AC, SORT1, HIF3A, MAPK4, TCP11L1, ZZEF1, DCAF7, DMWD, CLCA2, VAC14, CSPG5, STMN2, MLLT4, GALNT14, FGF12, MFAP5, SUMO3, HTR3A, GDF5, TSSK1B, CYP2A7P1, MARK1, ATP1B2, TBX6, PAX8, IL1R1, RALYL, OR2B2, TAAR3, C12orf32, IGHG1, LOC642131, DICER1, GLRA3, PPARD, HSPA4L, WNT2, VIPR2, CYP2C9, SRPX2, IGSF1, ALPK3, TFPI, KCNS3, MARCH8, FRMD4B, TACR3, FIGF, PDCD6, TNN, SPANXB1, SPANXB2, SPANXF1, RHBDD3, SPP2, PDE10A, ZNF224, FGL1, PGAM2, CADM4, APOBEC2, SLC9A5, GNAT1, ARHGEF16, SMARCA2, DNAH9, RBM26, WNT2B, KCNK2, NPBWR2, SP2, TMPRSS11D, DENND2A, TNIP3, STC1, DOCK6, ADAM5P, SYDE1, TNPO2, LRTM1, USH1C, PDE12, SRCAP, OR10J1, OR2H2, KCNJ8, RP11-257K9.7, DOCK5, TPD52L1, PAEP, GGA2, PHLDA3, HES2, MLL, CHRNA6, CIB2, PTPRF, TM7SF4, DAZ1, DAZ2, DAZ3, DAZ4, ALX1, OR2F1, OR2F2, PLAT, HGC6.3, WNT11, PGK2, SNAI2, COL4A6, PRUNE2, ANKS1B, LOC81691, FERMT2, TIMP3, CST8, CAPN6, IDUA, GPR32, AKR1B10, GRHL2, FBXO24, HSF4, IGHG1, HCN2, LRP12, ARHGEF15, UGT1A1, UGT1A10, UGT1A7, UGT1A8, GUCA2A, ITIH1, EGFR, UGT1A1, UGT1A10, UGT1A3, UGT1A4, UGT1A5, UGT1A6, UGT1A7, UGT1A8, UGT1A9, MYOG, TMSB15A, TLX1, EDNRA, LOC100289791, MDFI, ZER1, MYH15, CDH20, GPR63, LOC440345, LOC440354, LOC595101, LOC641298, SMG1, HOXC10, KRTAP1-1, ARSD, CPLX3, LMAN1L, IFNA4, ABCC1, SEMA3E, MRE11A, C1QL1, LIPF, TRIM9, BBOX1, LRRC17, WNT2B, CYP3A4, SI, ANO3, OBSL1, CHRD, MSX2, PSG1, FAM107A, LRRC37B2, ANKLE2, PAX2, UNC5B, ADCYAP1R1, HFE, SYT1, GJC2, LOC100293871, FGF8, ACRV1, NRXN1, GDPD2, RGS4, CELA2A, IFNW1, MLNR, RNF17, LAD1, GLRA2, RASL12, MAGOH2, C6orf54, ZNF214, IKBKG, AP4E1, ZNRF4, OSBPL10, C1orf175, TTC4, PCDHB3, ADRBK1, ITSN1, XAGE1A, XAGE1B, XAGE1C, XAGE1D, XAGE1E, CDH22, FARP2, MYT1, TNC, MUC5AC, SLC6A15, PP14571, SMR3A, SMR3B, RXRG, SNX1, GLP1R, C6orf155, ATP1A2, TFAP4,

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NFATC4, ADAMTS7, FOXL1, GPR17, SLC18A3, MYH6, BOK, FGA, TEAD4, GRM1, EDNRA, C8orf79, METTL7A, FOLH1, RAD54L, SOX11, CNOT3, NTS, MAPK12, DOCK6, DNAJC6, HS3ST3A1, LOC728395, TSPY1, TSPY3, PTH, LAMB4, ALDOB, FLG, MLANA, UBE2D4, LOC100287483, KRT20, POU1F1, SLCO1B3, CLTA, MECOM, C8orf71, SULT2A1, C6orf10, SLC27A6, PRKD1, SYNPO2L, THPO, GABRR1, CFTR, PPP2R3A, DCBLD2, ANP32A, ANP32C, ANP32D, LOC723972, XYLT1, STAB1, STAB1, SASH1, PID1, FUCA1, SASH1, LRRN3, LRRN3 or a combination thereof.

In another embodiment, the gene is ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-5/20/22, IL-9/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad2/3/4, PAI-1, SELP, ITFA8 , ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-5/13/20/22 , IL-9/11/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1 or a combination thereof. In another embodiment, the gene is SELP, ITFA8 , ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/1R/5/8/13/20/22, IL-9/11/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, Smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1 or a combination thereof.

In one embodiment of any one of the methods, uses, pharmaceutical composition or packages described herein, the gene is TNFSF4, ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/5/8/20/22, IL-9/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, Smad2/3/4, PAI-1, TNFSF4, SELP, ITFA8, ITGB1/3/5, CXCL5/7, a BMP6 gene, ITGA2/8, ITGβ1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/1R/5/8/13/20/22R, IL-9/11/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, type II BMPR, smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1, IL8R (CXCR1/2), Alpha tubulin, BMP2/4/7, MIS, TCF2, LFA-1, VLA-4, IL5R, IL13R, IL20R, ITGB2, IFN gamma, TNF alpha, NKTR, TEF, CLSTN2, LUC7L2, FABP7, TPTE, FSTL1, SF3B1, LIMS1, PDE5A, XPNPEP1, C5orf4, SPANXB1, SPANXB2, SPANXF1, KRT20, TBC1D1, GRHL2, C5orf4, SEPT6, KIAA1199, SSX2IP, TPM1, CDC14B, USP47, MMRN1, CTNNAL1, SMOX, ALOX12, GLRA3, CA2, GUCY1B3, RFPL1, CLEC1B, GNG11, TSPAN32, RGS10, CALD1, PRKAR2B, CYP4F11, CLCA3P, CELSR3, CDC14B, TPM1, SEPT6, PRKG1, MAX, CCDC93, ARMCX6, LOC653354, TUBB2B, HIST1H2AJ, MFAP3L, LIMS1, GNB5, GPRASP1, SRRT, C1orf116, FBXO7, PPM1A, GUCY1B3,CTDSPL, GNAS, IGF2BP3, TPM1, HIST1H2BK, DLG4, WDR48, CALD1, LOC157627, GNB5, ZNF415,ASAP2, PSD3, GNAS,POPDC3, NRGN, ABLIM3, XYLT1, PTGIS, ARHGEF10, PDGFA,PGRMC1, HIST1H2AC, GNAS, CLDN5,

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MAP2K2, TP63, DACH1, PPP5C, SLC26A1, NUDT7, KCNJ12, ENTPD7, SLC26A1, PRRG3, RGS6, ZBED2, FICD, ARHGAP1, ARHGDIA, SDHB, AMHR2, ABCA4, TCF20, BGN, CASP7, LPAR4, GNA12, CYP2W1, RAX, C4A, C4B, LOC100292046, LOC100294156, ELAVL4, PXN, ESR2, MYL10, EFS, TFF3, SRPK1, LOC441601, BIRC5, CCT8L2, PPAP2B, CMA1, APOA2, KDELR2, ASCL3, RUNX1, BUB1, SLC6A8, HNRNPC, HNRNPCL1, LOC440563, LOC649330, RIBC2, CLIC4, RAB17, SCML2, SPINLW1, ANK1, EDA2R, HTR4, CDC42EP4, KANK2, ANK1, SYN1, DUX3, DUX4, FRG2C, HPX-2, LOC100134409, LOC652119, LOC653543, LOC653544, LOC653545, LOC728410, PKNOX2, MLLT4, APOA2, PENK, GNAT1, FURIN, SEMA6A, EGFL6, HRH1, TSPAN1, DBC1, TRPC7, MDM2, GPR52, HAMP, PRSS2, GPR107, FLJ11292, FLJ20184, B4GALT1, NKX3-1, ASIP, EFCAB6, GPR20, CA5A, PLK4, TAAR5, SRPX2, CNTD2, AZGP1, TIMP3, RGS6, ADARB1, DYNC1I1, C10orf10, PDIA2, PITX3, HOXC13, LPAR3, CTRC, CTSL2, MUC8, AQP5, UGT1A1, UGT1A10, UGT1A4, UGT1A6, UGT1A8, UGT1A9, KCNQ2, CYP2A13, ZNF155, KIAA0892, ATP2A2, FGF5, FGF18, FUT2, SHROOM2, PRSS3, CREB3L1, MGAT2, PLCE1, MLXIPL, OR10H3, ABCB11, CD84, ARHGEF4, ORC1L, PCIF1, CD177, C1orf116, IFT122, C11orf20, DUSP13, C6orf208, PLA2G5, PRAMEF1, PRAMEF2, CYP4F8, KCNA1, MFAP4, C6, SLC4A3, IL1RAPL1, SERPINE1, ZCCHC14, POLR3G, C16orf68, FLJ14100, SMCHD1, ASCL1, FOXA2, SLC23A2, KLK13, MTSS1L, DNMT3L, RREB1, DNMBP, PKLR, C1orf106, CCDC134, MTSS1, CCDC40, HOXB1, SCNN1B, SEMA4G, RAPGEFL1, MAGEL2, PLSCR2, CHD2, PLCD1, C1orf116, CHRNA2, MBP, CDC42BPA, MYF6, PI15, LOC440895, SBF1, MAST1, GLT8D2, ERBB3, LOH3CR2A, AMH, HR, RDH8, PAWR, DRD3, CCT8, PRELP, SPOCK3, EPS8L3, NXN, SEMA4G, P2RY1, AVL9, TEK, MOGAT2, KLK7, MT1E, MT1H, MT1M, CLDN18, RHBDF2, SIX1, INPP5A, KCNMB3, MAP2K5, GPD1, LPO, LOC729143, MPRIP, WNT7A, RARG, CDH7, MBNL2, RASGRP2, RBMY2FP, MASP1, CASR, EGR4, APOC2, HECW1, HOXB3, IRF5, NNMT, AOC2, ESRRG, LPIN1, ACOT11, CCDC33, MBD2, ZNF323, NTRK2, TMEM151B, GPLD1, LENEP, HNF1B, NXPH3, ALDH1A3, PHF20L1, CKM, PARD6B, CRYGB, HAB1, LARGE, RAB40C, MPL, CHIT1, METTL10, DUS4L, PNLIPRP1, ELL, ST8SIA5, GRIN2B, MC4R, RTDR1, HDAC6, KCNJ13, CPSF1, SPANXC, CNOT4, LAMA2, SLC1A6, ABCA2, KLK11, GFRA3, CYP3A4, SLC1A3, ATP2B2, APBB2, VPS45, GHRHR, HOXD4, PRPH, ADCY2, LEFTY2, CYP1B1, PCP4, C8B, RANBP3, PDE6H, TRIM15, VGLL1, TRIM3, CRKL, ADH7, PSG3, GPR153, MFAP2, FGF13, NAPA, ALDH3A1, MCM10, TLE4, ITPR3, CCDC87, C9orf7, ACTC1, OBSL1, MAP2, CRYM, RNF122, SST, HLA-DRB6, SLC22A17, HSPG2, HIP1, GRIK2, UNKL, GPR144, KIR3DX1, NARFL, UCP3, PLXNA2, BTN1A1, ERCC4, CIITA, EGFR, KRT33A, CLTB, B3GALT5, AP3M2, GJC1, MYO3A, ARHGAP1, PPP2R3A, CLIC4, C20orf195, SIGLEC8, GPRC5A,

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IL13RA2, TRIM10, RTEL1, PRRX2, TSHB, TIMELESS, FMO1, KIF18A, KIAA1199, CALB2, MFAP3L, PTGER3, EPAS1, SQSTM1, TSPY1, CPM, DLGAP1, CYP4F11, TLX3, PCDHA10, TAOK2, ERC1, TBX2, KALRN, DICER1, PAPPA, KIF5A, DNAJC22, OTUB1, KIAA1644, SEZ6L2, PCNXL2, HMHB1, ERG, SNTB2, GJA5, AGTR2, GJA3, GCK, LRRC61, CNTF, ZFP91, ZFP91-CNTF, PDLIM4, MPPED2, IFNA10, ACTN2, VGLL1, GJA9, LDLR, ANK2, COL1A1, TIMP3, OTOF, AGXT, GLI2, TRMT61A, FOXD2, TMEM212, DENND2A, B3GALT1, SPAG11A, PRDM4, TF, ELF5, GSC2, EPB41L4B, GYG2, LYZL6, DCHS2, OBP2A, OBP2B, ANGPTL3, MYH11, NES, SLC17A1, RBM15B, CSH1, HTR5A, CYP3A7, HTR2A, KCNV2, TOX3, CLOCK, MAGEA6, FAM12A, COL4A3, S1PR2, NAT8, ACE2, SLC22A6, SLC13A2, MYH4, APBB2, RAP1GAP, SHOX2, SLCO1A2, ETV1, MAGEA12, PLA2G6, ADRA1A, SYT5, GPR161, SEMA3F, CYP3A43, HOMER2, KCNJ5, PPL, COL17A1, CSHL1, C9orf116, PARK2, UGT2B15, CDK6, FAM174B, CELA2A, CELA2B, SPDEF, EPB41, GAB1, SMR3A, PDE6G, COL5A1, ABCA6, DMD, CYLC2, CIDEA, RAG2, HIST1H2BN, FMO6P, MAOA, ANKRD53, HAPLN1, MT1M, EHD2, GAD2, CRISP2, CSN2, SULT1C2, PCDHGA3, SSX3, FGFR2, GPR161, ATN1, CHD5, A4GALT, MYBPH, CSHL1, NCAPH2, CAPN9, CNGB1, BCAM, DRD5, NR5A2, TEF, ELAVL2, DGKB, HTR7P, RHAG, GH2, COL4A6, BMP7, SOSTDC1, SOX14, TAS2R9, LPHN2, MAP1A, OSGIN2, SLC10A2, FAM13C, EMX1, FLJ40330, CHI3L1, CDH16, SPRR1A, LOX, CALCB, GABBR2, CPB2, RASL11B, CCDC81, RUNX1, CPA1, CLCNKA, CLCNKB, FHL5, THSD7A, TFAP2C, SPAG11B, CAP2, PODNL1, SSX4, SSX4B, G6PC, RPE65, TMEM222, KDR, CHP2, GPR64, TPM2, TCEB3B, E2F5, IL5RA, AOC3, ABCF3, CPN2, ACE, NRP2, INPP5J, SMAD9, FAM155A, GART, PIR, ZNF467, ITSN2, NR1D1, THRA, RP11-35N6.1, LAMB1, EPHB3, PLA2R1, RAPGEF4, DNAJC8, ARSJ, TRIM49, GC, IL12B, CDH2, ATXN3L, BTF3L1, BICC1, FAM186A, PTPRF, TRPC4, TCL6, CYP4A22, FUT6, MUC1, DKFZP434B2016, LOC643313, LDHA, LOC100131613, TRIM3, MLLT10, DZIP1, ANKRD34C, BUB1, CSPG5, FBLN1, GAD2, CLDN1, CHRNA3, SCN11A, TEX11, IL20RA, AKAP5, KBTBD10, MSTN, TLL2, NACAD, UNC93A, PTGER1, OLAH, NHLH2, SERPINA6, KRT17, KCNMA1, PRKCA, STS, LAMA1, GPR88, ACTN2, TREH, AKAP4, DKK4, PRICKLE3, IRS4, TRPV4, PCDH11Y, APBB2, SLCO2A1, DRD2, MTMR7, ZNF471, TF, NRIP2, ST6GALNAC5, COMT, PAH, LRRC19, PRKAR1B, HPR, PRDM5, NCRNA00120, LOC79999, ITSN2, CACNB2, GPR98, PREX2, FAM182B, LAMA4, ARVCF, HAS2, YOD1, PPP2R3A, COL4A1, RBM12B, GSTA3, FAM66D, OR10H2, PTHLH, ZNF674, KRT19, ACCN2, COL6A1, LOC100288442, LOC100289169, LOC728888, LOC729602, NPIPL2, NPIPL3, PDXDC2, SLC37A1, ATP6V1B1, PTN, ABI3BP, HR44, ZNF324B, ZNF584, HOXD13, ADH6, IFNA8, MYOZ2, NFATC4, ADAMTS7, FOXL1, GPR17,

SLC18A3, MYH6, BOK, FGA, TEAD4, GRM1, EDNRA, C8orf79, METTL7A, FOLH1, RAD54L, SOX11, CNOT3, NTS, MAPK12, DOCK6, DNAJC6, HS3ST3A1, LOC728395, TSPY1, TSPY3, PTH, LAMB4, ALDOB, FLG, MLANA, UBE2D4, LOC100287483, KRT20, POU1F1, SLCO1B3, CLTA, MECOM, C8orf71, SULT2A1, C6orf10, SLC27A6, PRKD1, SYNPO2L, THPO, GABRR1, CFTR, PPP2R3A, DCBLD2, ANP32A, ANP32C, ANP32D, LOC723972, XYLT1, STAB1, STAB1, SASH1, PID1, FUCA1, SASH1, LRRN3, LRRN3 or any combination thereof.

In another embodiment, the gene is TNFSF4, ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/5/8/20/22, IL-9/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, Smad2/3/4, PAI-1, TNFSF4, SELP, ITFA8, ITGB1/3/5, CXCL5/7, a BMP6 gene, ITGA2/8, ITGβ1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/1R/5/8/13/20/22R, IL-9/11/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, type II BMPR, smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1 or any combination thereof. In yet another embodiment, the gene is TNFSF4 , ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/5/8/20/22, IL-9/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, Smad2/3/4, PAI-1 or any combination thereof.

In one embodiment, laquinimod is administered orally. In another embodiment, laquinimod is administered daily.

In one embodiment, laquinimod is administered at a dose of less than 0.6 mg/day. In another embodiment, laquinimod is administered at a dose of 0.1-40.0 mg/day. In another embodiment, laquinimod is administered at a dose of 0.1-2.5 mg/day. In another embodiment, laquinimod is administered at a dose of 0.25-2.0 mg/day. In another embodiment, laquinimod is administered at a dose of 0.5-1.2 mg/day. In another embodiment, laquinimod is administered at a dose of 0.25 mg/day. In another embodiment, laquinimod is administered at a dose of 0.3 mg/day. In another embodiment, laquinimod is administered at a dose of 0.5 mg/day. In another embodiment, laquinimod is administered at a dose of 0.6 mg/day. In another embodiment, laquinimod is administered at a dose of 1.0 mg/day. In another embodiment, laquinimod is administered at a dose of 1.2 mg/day. In another embodiment, laquinimod is administered at a dose of 1.5 mg/day. In yet another embodiment, laquinimod is administered at a dose of 2.0 mg/day.

In one embodiment, the subject is a naïve subject. In another embodiment, the subject is naïve to laquinimod. In another embodiment, the subject has been previously administered laquinimod.

In another embodiment, the subject has been previously administered a multiple sclerosis drug other than laquinimod.

In an embodiment, the step of evaluating expression of the biomarker comprises normalization of the subject's gene expression. In another embodiment, the step of evaluating expression of the biomarker comprises comparing expression level in the subject relative to a reference value. In another embodiment, the reference value is based on the level of expression of the biomarker in a laquinimod Non-Responder population. In another embodiment, the reference value is based on the level of expression of the biomarker in a healthy control population. In yet another embodiment, the reference value is based on the level of expression of the subject at baseline.

In one embodiment, the subject is identified as a laquinimod responder if expression of the biomarker is higher than a reference value. In yet another embodiment, the subject is identified as a laquinimod responder if expression level of the biomarker is lower than a reference value.

In one embodiment, expression of the biomarker is evaluated in the blood of the subject. In another embodiment, expression of the biomarker is evaluated in the peripheral blood mononuclear cells (PBMCs) of the subject. In another embodiment, expression of the biomarker is evaluated prior to treatment with laquinimod.

In one embodiment, expression of the biomarker is evaluated after beginning treatment with laquinimod. In another embodiment, expression of the biomarker is evaluated one month after beginning treatment with laquinimod. In another embodiment, expression of the biomarker is evaluated 6 months after beginning treatment with laquinimod. In another embodiment, expression of the biomarker is evaluated 12 months after beginning treatment with laquinimod. In another embodiment, expression of the biomarker is evaluated 24 months after beginning treatment with laquinimod.

In one embodiment, if the subject is identified as a laquinimod responder, the subject is thereafter administered a pharmaceutical composition comprising laquinimod and a pharmaceutically acceptable carrier as monotherapy. In another embodiment, if the subject is identified as a laquinimod responder, the subject is thereafter administered a pharmaceutical composition comprising laquinimod and a pharmaceutically acceptable carrier in combination with another multiple sclerosis drug. In another embodiment, if the subject is identified as a laquinimod non-responder, the subject is thereafter administered a multiple sclerosis drug which is not laquinimod.

In one embodiment, the subject is a human patient.

The subject invention also provides laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein the subject has been identified as a laquinimod responder.

The subject invention also provides a pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein the subject has been identified as a laquinimod responder

The subject invention also provides laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is up-regulated and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

The subject invention also provides a pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is up-regulated and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

The subject invention also provides laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is suppressed and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

The subject invention also provides a pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is suppressed and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

The subject invention also provides a therapeutic package for dispensing to, or for use in dispensing to, a subject identified as a laquinimod responder afflicted with multiple sclerosis or presenting a clinically isolated syndrome, which comprises: a) one or more unit doses, each such unit dose comprising an amount of laquinimod, and b) a finished pharmaceutical container

therefor, said container containing said unit dose or unit doses, said container further containing or comprising labeling directing the use of said package in the treatment of said subject.

The subject invention also provides a therapeutic package for dispensing to, or for use in dispensing to, a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, which comprises: a) one or more unit doses, each such unit dose comprising an amount of laquinimod, and b) a finished pharmaceutical container therefor, said container containing said unit dose or unit doses, said container further containing or comprising labeling directing the use of said package in the treatment of said subject, wherein expression of a biomarker in the subject is suppressed or up-regulated and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

For the foregoing embodiments, each embodiment disclosed herein is contemplated as being applicable to each of the other disclosed embodiment. For example, the elements recited in the method embodiments can be used in the use and package embodiments described herein and vice versa.

A pharmaceutically acceptable salt of laquinimod as used in this application includes lithium, sodium, potassium, magnesium, calcium, manganese, copper, zinc, aluminum and iron. Salt formulations of laquinimod and the process for preparing the same are described, e.g., in U.S. Patent Application Publication No. 2005/0192315 and PCT International Application Publication No. WO 2005/074899, which are hereby incorporated by reference into this application.

A dosage unit may comprise a single compound or mixtures of compounds thereof. A dosage unit can be prepared for oral dosage forms, such as tablets, capsules, pills, powders, and granules.

Laquinimod can be administered in admixture with suitable pharmaceutical diluents, extenders, excipients, or carriers (collectively referred to herein as a pharmaceutically acceptable carrier) suitably selected with respect to the intended form of administration and as consistent with conventional pharmaceutical practices. The unit will be in a form suitable for oral administration. Laquinimod can be administered alone but is generally mixed with a pharmaceutically acceptable carrier, and co-administered in the form of a tablet or capsule, liposome, or as an agglomerated powder. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain

suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents flow-inducing agents, and melting agents.

Specific examples of the techniques, pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described, e.g., in U.S. Patent Application Publication No. 2005/0192315, PCT International Application Publication Nos. WO 2005/074899, WO 2007/047863, and 2007/146248.

General techniques and compositions for making dosage forms useful in the present invention are described-in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976); Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing Company, Easton, Pa., 1985); Advances in Pharmaceutical Sciences (David Ganderton, Trevor Jones, Eds., 1992); Advances in Pharmaceutical Sciences Vol 7. (David Ganderton, Trevor Jones, James McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James McGinity, Ed., 1989); Pharmaceutical Particulate Carriers: Therapeutic Applications: Drugs and the Pharmaceutical Sciences, Vol 61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal Tract (Ellis Horwood Books in the Biological Sciences. Series in Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson, Eds.); Modern Pharmaceutics Drugs and the Pharmaceutical Sciences, Vol. 40 (Gilbert S. Banker, Christopher T. Rhodes, Eds.). These references in their entireties are hereby incorporated by reference into this application.

Tablets may contain suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. For instance, for oral administration in the dosage unit form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, dicalcium phosphate, calcium sulfate, mannitol, sorbitol, microcrystalline cellulose and the like. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn starch, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, povidone, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, sodium benzoate, sodium acetate, sodium chloride, stearic acid, sodium stearyl fumarate, talc and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, croscarmellose sodium, sodium starch glycolate and the like.

Terms

As used herein, and unless stated otherwise, each of the following terms shall have the definition set forth below.

As used herein, "laquinimod" means laquinimod acid or a pharmaceutically acceptable salt thereof.

As used herein, an "amount" or "dose" of an agent, e.g., laquinimod as measured in milligrams refers to the milligrams of the agent, e.g., laquinimod acid present in a preparation, regardless of the form of the preparation. A "dose of 0.6 mg laquinimod" means the amount of laquinimod acid in a preparation is 0.6 mg, regardless of the form of the preparation. Thus, when in the form of a salt, e.g. a laquinimod sodium salt, the weight of the salt form necessary to provide a dose of 0.6 mg laquinimod would be greater than 0.6 mg (e.g., 0.64 mg) due to the presence of the additional salt ion.

As used herein, a "unit dose", "unit doses" and "unit dosage form(s)" mean a single drug administration entity/entities.

As used herein, "about" in the context of a numerical value or range means ±10% of the numerical value or range recited or claimed.

As used herein, "effective" or "therapeutically effective" when referring to an amount of laquinimod or a therapy regimen using laquinimod refers to the quantity or regimen of laquinimod that is sufficient to yield a desired therapeutic response. Efficacy can be measured by an improvement of a symptom of multiple sclerosis. Such symptoms can include a MRI-monitored multiple sclerosis disease activity, relapse rate, accumulation of physical disability, frequency of relapses, time to confirmed disease progression, time to confirmed relapse, frequency of clinical exacerbation, brain atrophy, neuronal dysfunction, neuronal injury, neuronal degeneration, neuronal apoptosis, risk for confirmed progression, visual function, fatigue, impaired mobility, cognitive impairment, brain volume, abnormalities observed in whole Brain MTR histogram, general health status, functional status, quality of life, and/or symptom severity on work.

As used herein, "clinical responsiveness" is a measure of the degree of a patients' response to an agent, e.g., laquinimod. Positive clinical responsiveness corresponds to a patient who responds favorably to and/or benefits from receiving laquinimod (a laquinimod responder) while negative clinical responsiveness corresponds a patient who responds unfavorably to and/or does not benefit from receiving laquinimod (a laquinimod non-responder).

As used herein, "a gene associated with" a process or a system, e.g., a gene associated with inflammatory response or a gene associated with hematological system, is a gene which plays a

role in that process or system. As an example, a gene associated with inflammatory response can be IL-1R, IL-8R, IL-22R, IL-9, TNFRSF4 or RORC.

Administering to the subject" or "administering to the (human) patient" means the giving of, dispensing of, or application of medicines, drugs, or remedies to a subject/patient to relieve, cure, or reduce the symptoms associated with a condition, e.g., a pathological condition. The administration can be periodic administration. As used herein, "periodic administration" means repeated/recurrent administration separated by a period of time. The period of time between administrations is preferably consistent from time to time. Periodic administration can include administration, e.g., once daily, twice daily, three times daily, four times daily, weekly, twice weekly, three times weekly, four times weekly and so on, etc.

"Treating" as used herein encompasses, e.g., inducing inhibition, regression, or stasis of a disease or disorder, e.g., Relapsing MS (RMS), or alleviating, lessening, suppressing, inhibiting, reducing the severity of, eliminating or substantially eliminating, or ameliorating a symptom of the disease or disorder. "Treating" as applied to patients presenting CIS can mean delaying the onset of clinically definite multiple sclerosis (CDMS), delaying the progression to CDMS, reducing the risk of conversion to CDMS, or reducing the frequency of relapse in a patient who experienced a first clinical episode consistent with multiple sclerosis and who has a high risk of developing CDMS.

"Inhibition" of disease progression or disease complication in a subject means preventing or reducing the disease progression and/or disease complication in the subject.

A "symptom" associated with MS or RMS includes any clinical or laboratory manifestation associated with MS or RMS and is not limited to what the subject can feel or observe.

As used herein, "a subject afflicted with multiple sclerosis" or "a subject afflicted with relapsing multiple sclerosis" means a subject who has been clinically diagnosed to have multiple sclerosis or relapsing multiple sclerosis (RMS), which includes relapsing-remitting multiple sclerosis (RRMS) and Secondary Progressive multiple sclerosis (SPMS).

As used herein, a subject at "baseline" is as subject prior to administration of laquinimod.

A "patient at risk of developing MS" (i.e. clinically definite MS) as used herein is a patient presenting any of the known risk factors for MS. The known risk factors for MS include any one of a clinically isolated syndrome (CIS), a single attack suggestive of MS without a lesion, the presence of a lesion (in any of the CNS, PNS, or myelin sheath) without a clinical attack, environmental factors (geographical location, climate, diet, toxins, sunlight), genetics (variation of genes encoding HLA-DRB1, IL7R-alpha and IL2R-alpha), and immunological components

(viral infection such as by Epstein-Barr virus, high avidity $CD4^+$ T cells, $CD8^+$ T cells, anti-NF-L, anti-CSF 114(Glc)).

"Clinically isolated syndrome (CIS)" as used herein refers to 1) a single clinical attack (used interchangeably herein with "first clinical event" and "first demyelinating event") suggestive of MS, which, for example, presents as an episode of optic neuritis, blurring of vision, diplopia, involuntary rapid eye movement, blindness, loss of balance, tremors, ataxia, vertigo, clumsiness of a limb, lack of co-ordination, weakness of one or more extremity, altered muscle tone, muscle stiffness, spasms, tingling, paraesthesia, burning sensations, muscle pains, facial pain, trigeminal neuralgia, stabbing sharp pains, burning tingling pain, slowing of speech, slurring of words, changes in rhythm of speech, dysphagia, fatigue, bladder problems (including urgency, frequency, incomplete emptying and incontinence), bowel problems (including constipation and loss of bowel control), impotence, diminished sexual arousal, loss of sensation, sensitivity to heat, loss of short term memory, loss of concentration, or loss of judgment or reasoning, and 2) at least one lesion suggestive of MS. In a specific example, CIS diagnosis would be based on a single clinical attack and at least 2 lesions suggestive of MS measuring 6 mm or more in diameter.

As used herein, a "multiple sclerosis drug" is a drug or an agent intended to treat clinically defined MS, CIS, any form of neurodegenerative or demyelinating diseases, or symptoms of any of the above mentioned diseases. "Multiple sclerosis drugs" may include but are not limited to antibodies, immunosuppressants, anti-inflammatory agents, immunomodulators, cytokines, cytotoxic agents and steroids and may include approved drugs, drugs in clinical trial, or alternative treatments, intended to treat clinically defined MS, CIS or any form of neurodegenerative or demyelinating diseases. "Multiple sclerosis drugs" include but are not limited to Interferon and its derivatives (including BETASERON®, AVONEX® and REBIF®), Mitoxantrone and Natalizumab. Agents approved or in-trial for the treatment of other autoimmune diseases, but used in a MS or CIS patient to treat MS or CIS are also included.

As used herein, a "naïve patient" is a subject that has not been treated with a multiple sclerosis drug as defined herein. Similarly, a patient or subject who is "naïve" to an agent, e.g., laquinimod, is a patient or subject that has not been treated with said agent.

As used herein, "in the blood of the subject" is represented by PBMCs, lymphocytes, monocytes, macrophages, basophils, dendritic cells or other cells derived from the subject's blood.

As used herein a "reference value" is a value or range of values that characterizes a specified population in a defined state of health.

A "pharmaceutically acceptable carrier" refers to a carrier or excipient that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio. It can be a pharmaceutically acceptable solvent, suspending agent or vehicle, for delivering the instant compounds to the subject.

It is understood that where a parameter range is provided, all integers within that range, and tenths thereof, are also provided by the invention. For example, "0.1-2.5 mg/day" includes 0.1 mg/day, 0.2 mg/day, 0.3 mg/day, 0.4 mg/day, 0.5 mg/day etc. up to 2.5 mg/day.

This invention will be better understood by reference to the Experimental Details which follow, but those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention as described more fully in the claims which follow thereafter.

Experimental Details

EXAMPLE 1: High-Through Output Gene Expression Ancillary Study for Phase III Clinical Trial ("ALLEGRO" or MS-LAQ-301) To Assess Effect of Laquinimod On Peripheral Blood Mononuclear Cells in Relapsing-Remitting Multiple Sclerosis

In a previous study by Gurevich et al. (Gurevich et al. 2010), *in vitro* molecular effects of laquinimod (LAQ) in peripheral blood mononuclear cells (PBMC) of healthy subjects and relapsing-remitting multiple sclerosis (RRMS) patients were characterized by gene expression microarrays. Gurevich et al. demonstrated that LAQ induced suppression of genes related to antigen presentation and corresponding inflammatory pathways. To further elucidate the molecular mechanism/s underlying the therapeutic effect of LAQ following treatment of patients displaying RRMS, the inventors performed gene expression microarray analysis of PBMCs from RRMS patients treated with LAQ as ancillary study to ALLEGRO clinical trial.

ALLEGRO Clinical Trial

ALLEGRO was a multinational (24 countries), multicenter (approximately 139 sites), randomized, double-blinded, parallel-group, placebo-controlled clinical trial conducted to evaluate the efficacy, safety and tolerability of daily oral administration of laquinimod 0.6 mg in subjects with relapsing remitting multiple sclerosis (RRMS) for a 24 months duration.

One thousand one hundred and six (1106) patients were equally randomized to either laquinimod 0.6mg or placebo and treated in a double-blind manner and baseline characteristics were balanced between groups. The primary endpoint of the study was the number of confirmed relapses during the double-blind treatment period, which corresponds to the annualized relapse rate (ARR - number of relapses divided by total exposure of all patients). Secondary endpoints included disability as measured by Expanded Disability Status Scale (EDSS) changes confirmed at 3 months, and cumulative number of gadolinium enhancing (GdE) and new/enlarging T2 MRI lesions.

Study Duration

Screening phase: 1 month.

Double blind treatment phase: 24 months of once-daily oral administration of daily dose of 0.6 mg laquinimod or matching placebo.

Upon blinded variance and power reassessment of the population progression (planned prior to first subject completes the 20 months of treatment), the double blind study duration may be extended to 30 months. This is planned in order to enhance the statistical power to detect the

effect of laquinimod on disability accumulation. The recommendation to extend the study duration is based on a pre-defined rule.

Study Design

Eligible subjects were equally randomized 1:1 into one of the following treatment arms:

1. Laquinimod capsules 0.6 mg: One 0.6 mg laquinimod capsule was administered orally once daily. The 0.6 mg laquinimod capsules contain 0.6 mg of Laquinimod Acid per capsule with meglumine, and were manufactured according to the method disclosed in PCT International Application Publication No. WO/2007/146248, published December 21, 2007 (see, page 10, line 5 to page 11, line 3).
2. Matching placebo for laquinimod arm: one capsule is administered once daily.

Subjects were evaluated at study sites for 12 scheduled visits of the double blind phase at months: -1 (screening), 0 (baseline), 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24 (termination/early discontinuation). In case of the 6 months extended study, subjects were evaluated at study sites at months 27 and 30 (termination/early discontinuation of extended study), in this case month 24 was a regular scheduled visit.

EDSS was assessed every 3 months, MSFC every 6 months, and MRI was performed annually in all patients. A subgroup of patients (n=189) underwent additional MRI scans at months 3 and 6. Subjects successfully completing the study were offered the opportunity to enter into a 1-year open label extension. Patients who discontinued the study underwent a final termination visit and were not further evaluated, except for those who discontinued due to adverse events.

The following assessments were performed at specified time points:

1. Vital signs were measured at each study visit.
2. A physical examination is performed at months -1 (screening), 0 (baseline) 1, 3, 6, 12, 18 and 24 (termination/early discontinuation core study). In case of the 6 months extended study, additional examination was performed at month 30 (termination/early discontinuation of extended study).
3. The following safety clinical laboratory tests were performed:
   a. Complete blood count (CBC) with differential – at all scheduled visits. A reticulocyte count was added to the CBC at months 0 (baseline) and 24/30 (termination/early discontinuation).

b. Serum chemistry (including electrolytes, liver enzymes, direct and total bilirubin and pancreatic amylase and CPK), and urinalysis – at all scheduled visits.

c. A rapid urine β-hCG test was performed in women of child-bearing potential at baseline (month 0) and at each scheduled study visit thereafter (at site).

d. β-hCG in women of child-bearing potential was performed at all scheduled visits.

e. Starting after visit Month 3 a rapid urine β-hCG test was performed in women of child-bearing potential every 28 (±2) days. The subject was contacted by telephone within 72 hours after the test was scheduled to be performed and asked specific questions regarding the test. In case of suspected pregnancy (positive urine β-hCG test result), the caller made sure that the study drug has been discontinued and the subject was instructed to arrive at the site as soon as possible with all study drugs.

4. Markers of inflammation (serum conventional C-reactive protein and fibrinogen) – at screening, baseline and all scheduled visits thereafter.

5. During the first 3 months periodical phone calls were placed by the site personnel every two weeks. A list of predefined questions relating to signs/symptoms suggestive of vascular thrombosis was presented to the subjects.

6. ECG was performed at months -1 (screening; additional recording, up to 30 minutes apart is performed if QT_c is less than 450 msec), (baseline; three recordings, 15 minutes apart), 1, 2, 3, 6, 12, 18 and 24 (termination/early discontinuation). In case of the 6 months extended study, ECG is performed at month 30 (termination/early discontinuation of the extended study).

7. Chest X-ray is performed at months -1 (screening), (if not performed within 7 months prior to the screening visit).

8. Adverse Events (AEs) are monitored throughout the study.

9. Concomitant medications are monitored throughout the study.

10. Neurological evaluations, including Expanded Disability Status Scale (EDSS), 25 foot walk test/Ambulation Index (AI), Functional systems (FS) are performed at months -1 (screening), 0 (baseline) and every 3 months during the study and the extended study period.

11. MS functional Composite (MSFC) was assessed at months -1 (screening) (three practices for training purposes only), at month 0 (baseline), 6, 12, 18 and 24 (termination/early

discontinuation). In case of the 6 months extended study, the last MSFC was performed at months 30 (termination/early discontinuation of the extended study).

12. Subject-reported fatigue was assessed by the Modified Fatigue Impact Scale (MFIS) at months 0, 6, 12, 18, and 24 (termination/early discontinuation). In case of the 6 months extended study, additional MFIS was performed at month 30 (termination/early discontinuation of the extended study).

13. The general health status was assessed by the EuroQoL (EQ5D) questionnaire at month 0 (baseline) and month 24 (termination/early discontinuation of the study). In case of the 6 months extended study, the last EuroQoL (EQ5D) was performed at month 30 (termination/early discontinuation of the extended study) instead of month 24.

14. The general health status was assessed by the Short-Form general health survey (SF-36) subject-reported questionnaire at month 0 (baseline) and every 6 months thereafter, until termination/early discontinuation.

15. The subject undewent 5 assessments of binocular low-contrast visual acuity using the 100%, 2.5% and 1.25% contrast level charts [Sloan letter or Tumbling-E] in each assessment, at months 0 (baseline), 6, 12, 18 and 24 (termination/early discontinuation). In case of extending the study for 6 months, additional binocular low-contrast visual acuity assessment is performed at month 30 (termination/early discontinuation of the extended study).

16. Serum samples were collected from all subjects in order to investigate the potential mechanism of action of laquinimod and additional biomarkers of inflammation and potential biomarkers of MS disease at months: 0, 1, 12 and 24. In case of extending the study for 6 months the last serum sample is performed at month 30 (termination/early discontinuation of the extended study) instead of month 24.

17. The subjects underwent 3 MRI scans at months 0 (baseline), 12 and 24 (termination/early discontinuation). In case of the 6 months extended study, an additional MRI was performed at month 30 (termination/early discontinuation of the extended study).

18. Population PK study (PPK): Blood samples for PPK evaluation were collected from all subjects at months 1, 12 and 24. In case of extending the study for 6 months the last PPK evaluation was performed at month 30 (termination/early discontinuation of the extended study) instead of month 24.

19. Relapses were confirmed/monitored through the study. Since the "in study" relapse definition must be supported by an objective neurological evaluation, a neurological deficit must sustain long enough to eliminate pseudo-relapses. Therefore, in this clinical trial, a relapse was the appearance of one or more new neurological abnormalities or the reappearance of one or more previously observed neurological abnormalities wherein the change in clinical state lasts at least 48 hours and is immediately preceded by an improving neurological state of at least thirty (30) days from onset of previous relapse.

20. The allowed treatment for a relapse was intravenous Methylprednisolone 1 gr/day for up to 5 consecutive days.

Inclusion/Exclusion Criteria

Inclusion Criteria

1. Subjects must have a confirmed and documented diagnosis as defined by the Revised McDonald Criteria (Polman, 2005), with relapsing-remitting disease course.
2. Subjects must be ambulatory with converted Kurtzke EDSS score of 0-5.5.
3. Subjects must be in a stable neurological condition and free of corticosteroid treatment [intravenous (iv), intramuscular (im) and/or per os (po)] 30 days prior to screening (month -1).
4. Subjects must have experienced one of the following:
   a. At least one documented relapse in the 12 months prior to screening.
   b. At least two documented relapses in the 24 months prior to screening.
   c. One documented relapse between 12 and 24 months prior to screening with at least one documented T1-Gd enhancing lesion in an MRI performed within 12 months prior to screening.
5. Subjects must be between 18 and 55 years of age, inclusive.
6. Subjects must have disease duration of at least 6 months (from the first symptom) prior to screening.
7. Women of child-bearing potential must practice an acceptable method of birth control. Acceptable method of birth control in this study include: surgical sterilization, intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, partner's vasectomy or double barrier method (condom or diaphragm with spermicide).

8. Subjects must be able to sign and date a written informed consent prior to entering the study.

9. Subjects must be willing and able to comply with the protocol requirements for the duration of the study.

Exclusion Criteria

1. Subjects with progressive forms of MS.

2. An onset of relapse, unstable neurological condition or any treatment with corticosteroids [(iv), intramuscular (im) and/or per os (po)] or ACTH between months -1 (screening) and 0 (baseline).

3. Use of experimental or investigational drugs, and/or participation in drug clinical studies within the 6 months prior to screening.

4. Use of immunosuppressive including mitoxantrone (Novantrone®) or cytotoxic agents within 6 months prior to screening visit.

5. Previous use of any one of the following: natalizumab (Tysabri®), caldribine, laquinimod.

6. Previous treatment with glatiramer acetate (copaxone®) Interferon-β (either 1a or 1b) or intravenous immunoglobulin (IVIG) within 2 months prior to screening visit.

7. Systemic corticosteroid treatment of ≥30 consecutive days duration within 2 months prior to screening visit.

8. Previous total body irradiation or total lymphoid irradiation.

9. Previous stem cell treatment, autologous bone marrow transplantation or allogenic bone marrow transplantation.

10. A known history of tuberculosis.

11. Acute infection two weeks prior to baseline visit.

12. Major trauma or surgery two weeks prior to baseline.

13. Use of inhibitors of CYP3A4 within 2 weeks prior to baseline visit (1 month for fluoxetine).

14. Use of amiodarone within 2 years prior to screening visit.

15. Pregnancy or breastfeeding.

16. A ≥3xULN serum elevation of either ALT or AST at screening.

17. Serum direct bilirubin which is ≥2xULN at screening.

18. A QTc interval which is 450 msec (according to machine output) obtained from:

    a. Two ECG recordings at screening visit, or

    b. The mean value calculated from 3 baseline ECG recordings.

19. Subjects with clinically significant or unstable medical or surgical condition that would preclude safe and complete study participation, as determined by medical history, physical examination, ECG, laboratory tests or chest X-ray. Such conditions may include:

    a. A cardiovascular or pulmonary disorder that cannot be well-controlled by standard treatment permitted by the study protocol.

    b. A gastrointestinal disorder that may affect the absorption of study medication.

    c. Renal or metabolic diseases.

    d. Any form of chronic liver disease.

    e. Known human immunodeficiency virus (HIV positive status.

    f. A family history of Long- QT syndrome.

    g. A history of drug and/or alcohol abuse.

    h. Major psychiatric disorder.

20. A known history of sensitivity to Gd.

21. Inability to successfully undergo MRI scanning.

22. Known drug hypersensitivity that would preclude administration of laquinimod, such as hypersensitivity to: mannitol, meglumine or sodium stearyl fumarate.

Ancillary High-Through Output Gene Expression Study

The goal of this ancillary study was to characterize gene expression changes and corresponding biological mechanisms induced in PBMC of RRMS patients by LAQ treatment. According to ALLEGRO clinical trial inclusion criteria, 25 patients were randomly assigned to receive LAQ (n=13, age 38.8±2.3 years, female/male ratio: 8/5) or placebo (n=12, age 37.2±3.4 years, female/male ratio: 8/4).

Peripheral blood samples were obtained from RRMS patients at baseline before start of LAQ treatment or placebo, after 0, 1, 6 and 24 month of treatment (visit 0, 1, 6 and 7 according to ALLEGRO clinical trial protocol correspondently) for gene microarray analysis.

Briefly, 1) Peripheral blood mononuclear cells (PBMC) were obtained from RRMS patients that participated in ALLEGRO and were treated daily with 0.6 mg LAQ or placebo. PBMC were subjected for gene expression analysis (HU-133A-2-Affymatrix arrays) at baseline and at 1 and 6 months of LAQ treatment; 2) Data was analyzed by Partek Genomics Solution software. Most informative genes (MIGs) were defined as those that differentiated between groups with $p<0.01$. Gene functional annotation, enrichment and pathway analysis were performed by Ingenuity software. For each time point, genes that changed in placebo group were excluded from further analysis; and 3) Verification of LAQ related mechanism was performed by Western blot.

LAQ was found to induce a differential gene expression of 354 MIGs at 1 month and 1562 MIGs at 6 months of treatment.

This study shows that LAQ down-regulates genes associated with adhesion, migration and chemotaxis of PBMC either directly or via TGFb suppression. These effects were observed after 1 and strengthened after 6 month of LAQ treatment. LAQ also down-regulates PAI-1 suggesting activation of fibrinolysis and possibly subsequent neuroprotection. Both effects can contribute to amelioration of MS clinical symptoms.

RNA isolation and hybridization

PBMC were extracted from 15 ml peripheral blood, separated by Ficoll–Hypaque gradient. Total RNA was extracted using both Trizol (Invitrogen, USA) and Phase-Lock-Gel columns (Eppendorf, Germany) including a DNase digestion step. RNA integrity was assessed by RNA Experion automated electrophoresis system (Bio-Rad Laboratories, Hercules, California).

Probe synthesis using 3 μg total RNA, hybridization, detection, and scanning was performed according to the standard Affymetrix, Inc. USA protocols; cDNA was synthesized using the Two-Cycle cDNA Synthesis Kit (Affymetrix, Inc., USA), and in-vitro transcription performed with the GeneChip IVT Labeling Kit (Affymetrix, Inc., USA). The biotin-labeled IVT–RNA was hybridized to HG-U133A-2 arrays containing 18,400 gene transcripts, each corresponding to 14,500 well-annotated human genes, washed in a GeneChip Fluidics Station 450 (Hewlett Packard, USA, GeneArray-TM scanner G2500A) and scanned according to the manufacturer's protocol (Affymetrix, Inc., USA).

Data analysis

Data analysis was performed on Partek Genomics Solution software (www.partek.com; Partek Incorporated, St. Louis, MO). Expression values were computed from raw CEL files by applying the Robust Multi-Chip Average (RMA) background correction algorithm. RMA correction included: 1) values background correction; 2) quintile normalization; 3) log2

transformation; and 4) median polish summarization. The ANOVA, Repeated Measures and correlation analysis implicated in Partek software ware applied to evaluate LAQ effects. Most informative genes MIGs were defined as those that differentiated between experimental groups with $p<0.01$. All p-values were calculated for False Discovery Rate (FDR) multiple test correction at $p=0.05$.

Additionally, significance of individual genes was tested by parametric T-test and non parametric Mann-Whitney test using Bootstrapping approach based on repeated permutations of the data with 5% FDR for multiple testing.

Gene functional annotation, enrichment, and pathway analyses to identify the leading biological pathways that operated under LAQ treatment were performed by Ingenuity Pathways Analysis software (www.ingenuity.com). Enrichment was defined as significantly ($p<0.05$) higher proportion of genes than expected by chance in a given gene set.

Western blot analysis

For verification of key genes on protein level Western blot analysis was performed. Supernatant was collected and protein concentration was determined using a Bradford assay (Pierce, Rockford, IL, USA) according the manufacturer's guidelines. Equal amounts of protein were suspended in sample buffer and boiled for 5 min. Cell lysates were resolved on 10% SDS-polyacrylamide gel electrophoresis (PAGE). Gels were transferred to a Nitrocellulose membrane (Amersham, Buckinghamshire, UK), blocked with 1% BSA in Tris-buffered saline Tween (TBST) buffer (20 mM Tris, 137 mM NaCl and 0.1% Tween 20) and incubated with primary antibody overnight at 4°C. After washing three times with TBST buffer, blots were incubated with alkaline peroxidase-conjugated secondary antibody. Antibodies were diluted in the blocking solution. The blots were then washed three times with TBST buffer and analyzed by standard chemiluminescence (Supersignal Kit, Pierce, Rockford, IL, USA) according to the company's protocol.

Results

According to ancillary study aims, 72 blood samples were collected. The number of samples and corresponding demographical data is presented in Table 1.

Table 1. Clinical and demographical data of subjects

Visit(Month)	**0(0)**	**1(1)**	**4(6)**	**7(24)**
N of patients	21	23	17	11
LAQ(N)	12	13	12	8

Placebo(N)	9	10	5	3
age	38.07±2.20	36.66±1.93	38.17±2.39	40.25±2.84
N(%) male	7/21(33.33%)	8/23(34.78%)	7/17(41.18%)	5/11(45.45%)
N(%) female	14/21(66.67%)	15/23(65.22%)	10/17(58.82%)	6/11(54.55%)
LAQ	**N(%) male**	5/12(41.67%)	5/13(38.46%)	5/12(41.67%)
	N(%) Female	7/12(58.33%)	8/13(61.54%)	7/12(58.33%)
Placebo	**N(%) male**	2/9(22.22%)	3/10(30.00%)	2/5(40.00%)
	N(%) Female	7/9(77.78%)	7/10(70.00%)	3/5(60.00%)

ANOVA analysis

ANOVA analysis was used to compare PBMC gene expression after 1, 6 or 24 month of LAQ treatment with baseline gene expression.

For each time point inventors performed analysis source of variation in dataset. (Fig.1). Age, gender and batch effects were considered as confounders regarding LAQ or Placebo related changes. For each time point genes associated with Placebo effect were evaluated and excluded from further analysis.

Table 2 below shows number of genes significantly changed by ANOVA test in each time point as compared with baseline.

Table 2. Number of LAQ related MIGs according to ANOVA p values.

Time Point	Visits according to protocol	# of genes p<0.01	Down regulated	Up-regulated	FDR
1 month	1	354	348	6	No
6 month	4	1562	1552	10	43
6 and 24 month	4 and 7	2922	2911	11	1564

Table 3 and Table 4 below shows the main biological pathways and functions affected by LAQ.

Table 3. Main biological pathways and functions affected by LAQ

After one month of treatment	**After six months of treatment**

function	pathway	genes (#)	p-value	function	pathway	genes (#)	p-value
Inflammatory response	Adhesion of phagocytes	9	$1.2*10^{-3}$	Development	G protein Coupled Receptor Signaling	73	$3.1*10^{-5}$
	Chemotaxis of Neutrophils	4	$6.0*10^{-3}$		Arachidonic Acid metabolism	18	$2.2*10^{-3}$
	Transmigration of leukocytes	8	$1.9*10^{-3}$		TGFB signaling	14	$4.3*10^{-2}$
	Caveolar mediated endocytosis	8	$1.8*10^{-4}$	Inflammatory response	Leukocyte Extravasation Signaling	29	$9.4*10^{-3}$
	Clathrin mediated endocytosis	12	$2.1*10^{-4}$		Caveolar mediated endocytosis	13	$2.1*10^{-2}$
Hematological system	Aggregation of blood platelets	18	$3.5*10^{-10}$	Cell signaling	Adhesion of cells	119	$2.4*10^{-5}$
	Activation of blood platelets	13	$1.4*10^{-8}$		Neuro-transmission	56	$2.1*10^{-5}$
	Aggregation of blood cells	19	$2.6*10^{-8}$	Hematological system	Intrinsic prothrombin activation pathway	6	$6.2*10^{-2}$
	Coagulation of blood	14	$7.4*10^{-7}$		Coagulation system	7	$7.4*10^{-2}$

Table 4. Main biological pathways and functions affected by LAQ

After one month of treatment	**After six months of treatment**

function	pathway	genes (#)	p-value	function	pathway	genes (#)	p-value
Inflammatory response	TGFb signaling	10	$3.2*10^{-3}$	Inflammatory response	TGFb signaling	14	$3.7*10^{-2}$
					IL-12 signaling	11	$3.2*10^{-3}$
Cellular Movement	Adhesion & migration of phagocytes	9	$1.2*10^{-3}$	Cellular movement	Invasion of cells	120	$5.6*10^{-5}$
	Chemotaxis of neutrophils	4	$6.0*10^{-3}$		Adhesion of cell	119	$2.4*10^{-5}$
	Transmigration of leukocytes	8	$1.9*10^{-3}$		Leukocyte extravasation signaling	31	$4*10^{-3}$

The majority of genes that showed significant changes at each time points were down regulated. The functional enrichment analysis of 354 genes affected after 1 month of treatment showed suppression of 50 molecules associated with different mechanisms of inflammatory response (p value from $3.4*10^{-10}$ to $1.1*10^{-2}$). This included for example suppression of adhesion of phagocytes ($p=1.2*10^{-3}$) and chemotaxis of neutrophils ($p=6.0*10^{-3}$) based on suppression of TGFB1, ITGB1, ITGB3, ITGB5 and CXCL5, ITGB1, MMP1, TGFB1 correspondently. The most significant canonical pathways are suppression of Caveolar and Clatrin mediated Endocytosis Signaling ($p=1.8*10^{-4}$ and $2.1*10^{-4}$). The interesting findings are suppression of PTCR and CD84 that function in adhesion interaction between T lymphocytes and accessory cells.

As shown in Table 2 the number of genes significantly affected by LAQ ($p<0.01$) changed from 354 to 1562 between 1 and 6 months of treatment, and 43 genes passed stringent FDR criteria for 6 months of treatment (Fig.2A). Total 260 genes out of 1562 were related to suppression of Cellular movement functions (p value of enrichment from $4.6*10^{-7}$ to $5.4*10^{-3}$). G protein Coupled Receptor Signaling ($p=3.1*10^{-5}$), Arachidonic Acid metabolism ($p=2.2*10^{-3}$), Leukocyte Extravasation Signaling ($p=9.4*10^{-3}$), Caveolar mediated endocytosis Signaling ($p=2.1*10^{-2}$), TGF beta Signaling ($p=4.3*10^{-2}$), Adhesion of cells ($p=2.4*10^{-5}$),

Neurotransmission ($p=2.1*10^{-5}$), Intrinsic prothrombin activation pathway ($p=6.2*10^{-2}$) and Coagulation system ($p=7.4*10^{-2}$) were the most significantly down-regulated canonical pathways after 6 months of treatment.

The number of patients involved in analysis at 24 months of treatment was relatively low, thus in order to improve statistical power, the inventors combined data from 6 and 24 months which resulted in evaluation of 2922 genes with $p<0.01$ and 1564 genes that passed FDR criteria (Fig.2B). Due to high statistical significance of combined 6 and 24 months LAQ signature the most detailed functional analysis was applied.

LAQ down-regulates expression of migration/adhesion molecules

Functional analysis of 1564 genes that passed FDR criteria after more than 6 months of treatment showed significant enrichment of down-regulated genes (n=305) related to different kind of cellular movement mechanisms with p values from $1.5*10^{-3}$ to $4.5*10^{-14}$. This included for example suppression of cell migration function (n=233, $p=4.5*10^{-14}$) and chemotaxis (n=78, $p=4.3*10^{-5}$).

LAQ significantly down-regulated a range of Metalloproteinase family members such as MMP1, MMP14, MMP16, MMP24, MMP25, MMP26, MMP28, ADAM12 and ADAM22. Several Integrin and chemokine related genes were down-regulated upon treatment of LAQ: ITGB1, ITGB5, ITGB6, ITGA8, ITGB8, and GPIIB-III3 (fibrinogen receptor), CXCL4, CCL14, CCL18, CCXCR1 (XCR1), CXCL7 (PPBP).

These results are in line with previous studies reporting that LAQ interferes with the migratory capacity of T cells in mice with EAE (Wegner et al., 2010, Jadidi-Niaragh et al., 2011).

LAQ down-regulates pro-inflammatory constituents

In addition to suppression of cell migration ability, treatment of LAQ demonstrated significant down-regulation of IL-1R, IL-8R and IL-22R, IL-9, TNFRSF4, and RORC (RORgamma), all of which are inflammation-related genes that are known to play a role in EAE (Jadidi-Niaragh et al., 2011). Recently, it has been shown that IL-9 is important for T-cell activation and differentiation in autoimmune inflammation of the CNS, and that IL-9-/- mice developed significantly less severe EAE than their WT counterparts (Li et al., 2011). The results show reduced expression of SOCS (suppressor of cytokine signaling), a negative regulator of immune response, which is indirectly regulated by TGFb1 and ICOSLG (inducible T-cell co-stimulator ligand). In correlation with down-regulation of the pro-inflammatory constituents, LAQ treatment significantly reduced the expression of CSF1, CSF2 and CSF3 and indirectly affected FoxP3 expression. ROR (RORgamma) can directly interact with FoxP3. However, the functional

consequence of this interaction is not clear because none of the previous studies on LAQ effect described an effect on Treg. Clatrin and Caveolar–mediated Endocytosis pathways are significantly suppressed ($p=5.0*10^{-4}$ and $p=5.9*10^{-4}$) after 1 month of treatment.

TGFB1 related mechanism

6 months or longer treatment of LAQ induced significant suppression of genes related to the TGFB pathway ($p=1.9*10^{-2}$) (Fig. 3)

TGFB is a potent regulatory cytokine with diverse effects on hematopoietic cells. The pivotal function of TGFB in the immune system is to maintain tolerance via the regulation of lymphocyte proliferation, differentiation, and survival. Among T cells, CD4+CD25+FOXP3+ T regs contain the main source of TGFB that suppresses immune responses in inflammatory sites. Defects in TGFB1 expression or its signaling in T cells correlate with the onset of several autoimmune diseases. It has been shown previously that besides its anti-inflammatory role, TGFB paradoxically acts as a pro-inflammatory cytokine and induces IL-17-producing pathogenic T helper cells (Th IL-17 cells) during an inflammatory response in which IL-6 is produced (Mirshafiey and Mohsenzadegan, 2009) (Fig.4). Consistent with the proposed pro-inflammatory role of TGFB our analysis showed down-regulation of several TGFB –related genes and its downstream signaling components including: LTBP1 (latent transforming growth factor beta binding protein 1), Type I receptor, Smad2/3, Smad4, TCF [hepatocyte nuclear factor 4 alpha (HNF4A)] and PAI-1 (Fig.3).

Western blot analyses in four out of five patients who received 6 months of LAQ treatment verified down-regulation of TGFB1 protein level by 20-50%, as shown by quantification of band intensities normalized against Tubulin (Figs. 5A and 5B).

LAQ induced down-regulation of Serpine 1 [(Plasminogen activator inhibitor 1(PAI-1)] and other members of the coagulation system

While anti-inflammatory properties of LAQ were previously reported (Gurevich et al., 2010, Brück and Wegner, 2011), the current study demonstrated down-regulation of several members of the coagulation pathway including F2 (thrombin), F7 (factor VII), F10 (factor X), FGB (fibrinogen beta-chain), TFPI [(tissue factor pathway inhibitor (lipoprotein-associated coagulation inhibitor)], Serpine 1 [plasminogen activator inhibitor (PAI-1)] and also two other members of the Serpine 1 family (SerpinA3 and SerpinB3). PAI-1 inhibits the serine proteases tissue plasminogen activator (tPA) and uPA/urokinase, thus it is an inhibitor of fibrinolysis, the physiological process that degrades blood clots. Although the tPA-plasmin cascade promotes neurodegeneration in excitotoxin-induced neuronal death, it has been demonstrated to have a

protective role in inflammatory conditions with BBB disruption by removing fibrin, which exacerbates axonal injury (Gveric et al., 2003). Moreover, in the mouse model of MS, EAE incidence and clinical severity were reduced in PAI-1-/- mice, where clinical relapses were absent in PAI-1-/- mice and the subsequent reduction in neuroinflammation was coupled with a higher capacity for fibrinolysis in spinal cord samples from PAI-1-/- mice, in association with increased tPA activity (East et al., 2008).

Importantly, consistent with our gene expression results, which shows significant down-regulation of PAI-1, the Western blot analysis shown in Fig.6 demonstrates reduced expression of PAI-1 protein by 30-50% in four out of five patients after 6 months of LAQ treatment. The quantification of band intensities were normalized against tubulin. Previous gene expression analysis of PBMCs treated *in vitro* with LAQ, also showed significant down-regulation of PAI-1 (Gurevich et al., 2010). These results suggest positive correlation between LAQ-induced down-regulation of TGFB1 and PAI-1 expression and implicate LAQ in suppression of the neuro-degenerative role of PAI-1, as demonstrated by East et al., 2008 and Gveric et al., 2003. The proposed mechanism of LAQ effects on PBMS is shown in Fig. 8A and Fig. 8B.

Correlation and Repeated measures analysis.

In ANOVA model each patients has to be independent under each condition. However in repeated measures algorithm the independence requirement is removed and each patients can repeatedly tested in different condition and responses from the same patients are correlated. Repeated measures increase statistical power and thus fewer subjects are needed to have adequate power. The inventors applied repeated measures analysis to evaluated effect of LAQ in same patients across all visits (28 microarrays related to 7 patients). First, using this approach the inventors evaluated Placebo effects and excluded placebo related genes from further analysis. The effect of LAQ realized in significant changing of 174 genes that pass FDR criteria with $p<0.0004$. Functional analysis of this gene list confirmed ANOVA results and among other included PTCRA, ITGB3, ITGA2B, ITGB5, PF4 and TGFB1 genes. The same of those gene profiles demonstrated in Fig. 7

Summary

In vivo effects of LAQ on PBMC showed down-regulation of genes as shown in Tables 3 and 4, including genes involving cell motility, adhesion, chemotaxis, IL1 and IL8 mediated inflammation, and Clatrin and Caveolar–mediated Endocytosis pathways, etc.

Functional enrichment analysis of most informative genes at 1 month of LAQ treatment demonstrated down-regulation of genes associated with inflammatory response, genes

associated with TGFb signaling including TGFb1, TGFb1I1 and LTBP1 (p value range = $3.8*10^{-4}$ to $6.7*10^{-3}$), (see Table 4) and other genes associated with cellular movement and migration (TNFSF4, SELP, ITGA8, ITGB1/3/5, CXCL5/7 and BMP6 genes).

Suppression of inflammation was further strengthened after 6 months of LAQ treatment, where there was suppression of large number of genes associated with adhesion, migration and leukocyte extravasation signaling (ITGA2/8, ITGb1/3/4/5/6, ITGBL1, MMP16/24/26/28 and ADAM12/18/22) accompanied by suppression of IL- 1/5/8/13/20/22R, IL-9/11/12/36, TNFRSF11A/B, and IFNA4/8/10/17. Notably, LAQ treatment also down-regulated TGFB expression including its downstream signaling constituents (LTBP4, MEK1/2, TGFB type I receptor and smad2/3/4). Laquinimod treatment down-regulated TGFb expression including its associated signaling constituents (LTBP4, type II BMPR and smad1/4/5/6/8) and the NFkB signaling constituents (IL-1, IL-1R and IKKg) (see, Figure 9A). Interestingly, the final downstream affected molecule in the TGFb pathway is the ITGB1 constituent of several Integrins that participates in rolling, adhesion, activation and locomotion and thereby regulates cellular movement in concert with CCL19, MMPs and ADAMs. The suppression of TGFB and ITGB1 was confirmed by Western blot (see Figure 5). The proposed mechanism of Laquinimod effects on PBMC is depicted in Figure 8A and Figure 8B.The underlying mechanism of LAQ treatment is characterized by down-regulation of Serpine 1 (Plasminogen activator inhibitor 1, PAI-1), a potent inhibitor of fibrinolysis and the final downstream molecule affected in the TGFB pathway, and other members of the coagulation system. These results suggest that in addition to its ability to modulate cytokines expression and adhesion/migration, LAQ also modulates the coagulation pathway, contributes to fibrinolysis (by effective fibrin removal) and thereby reduces neuronal damage. The majority of changes described in this report could be explained by considerable suppression TGFB1 mechanism.

Conclusion

- Laquinimod suppresses inflammation as shown by down-regulation of genes of pro-inflammatory cytokines, TGFb and NFkB pathways.
- Laquinimod suppresses the entire set of genes associated in the multistep paradigm of leukocyte extravasation suggesting its capability to inhibit infiltration of inflammatory cells to the CNS.
- These effects on inflammation and cell movement occurred either directly or via TGFb suppression were observed after one month and strengthened after six months of Laquinimod treatment.

- The down-regulation of TGFb, NFkB and cellular movement components by Laquinimod strongly suggests diminished CNS infiltration and subsequent reduction in axonal damage which may contribute to the therapeutic benefits of laquinimod in amelioration of MS clinical symptoms.

EXAMPLE 2: The Role Of Laquinimod In Modulation Of The Immune Response In Relapsing-Remitting Multiple Sclerosis: Lessons From Gene Expression Signature.

Abstract

The inventors analyzed the molecular pathways induced by LAQ treatment in patients that participated in the ALLEGRO trial using gene expression microarray analysis. Blood transcriptional changes after one and six months of treatment were compared to baseline to identify LAQ induced MIGs ($p<0.01$) and operating pathways.

The inventors identified 354 MIGs at one month and 1562 MIGs at six months of treatment. LAQ treatment effects were enhanced by duration of treatment and characterized by down-regulation of inflammatory responses via TGFb and NFkB signaling in combination with suppression of genes associated with cellular movement including adhesion, migration and leukocyte extravasation signaling like integrins, chemokines and metalloproteinases with further down-regulation of genes encoding pro-inflammatory cytokines.

These results demonstrate that LAQ acts via suppression of inflammation mainly through arrest of leukocytes extravasation and thereby could contribute to amelioration of disease activity in RRMS patients.

1. Introduction

LAQ was demonstrated to inhibit the development of acute experimental autoimmune encephalomyelitis (EAE) and to reduce EAE clinical score in mice treated after disease onset (Brück and Wegner, 2011; Brunmark et al., 2002; Jolivel et al., 2013; Ruffini et al., 2013; Schulze-Topphoff et al., 2012; Wegner et al., 2010). Clinically, LAQ demonstrated about 40% reduction in the cumulative number of gadolinium enhanced lesions in brain MRI in 106 RRMS patients as compared to 102 placebo treated RRMS patients (Comi et al., 2008). Recently, the Assessment of Oral Laquinimod in Preventing Progression in Multiple Sclerosis (Filippi et al., 2014) study demonstrated that LAQ treatment modestly decreased annualized relapse rate, slowed progression of disability and prevented white and gray matter atrophy in RRMS patients treated for 24 months (Comi et al., 2008; Filippi et al., 2014).

The mechanisms by which LAQ suppresses the development of EAE involve modulation of Th1/Th2 response, interference with the migration capacity of T cells (Bruck and Vollmer, 2013; Brück and Wegner, 2011; Wegner et al., 2010; Yang et al., 2004; Zou et al., 2002), and prevention of inflammation-induced synaptic alterations occurring in EAE (Ruffini et al., 2013). In addition, in MS patients, it has been reported that LAQ modulates B cells and their regulatory effects on T cells (Toubi et al., 2012), and down-regulates immunogenicity of dendritic cell (Jolivel et al., 2013).

In a previous study (Gurevich et al., 2010), the inventors characterized the molecular effects of LAQ in-vitro in separated immune cells subtypes obtained from RRMS patients using gene expression microarrays. The inventors demonstrated that LAQ induced suppression of genes related to antigen presentation and corresponding inflammatory pathways involving NFkB signaling, pleiotrophin-induced inflammatory cytokines, chemokine and toll like receptor signaling, down-regulation of Th2 response in CD14+ macrophages and CD4+ T cells, suppression of proliferation in CD8+ T cells, and suppression of antigen presentation and adhesion in CD19+ B cells via suppression of NFkB pathway.

To further elucidate the molecular mechanisms underlying the therapeutic effects of LAQ in RRMS, the inventors performed high throughput gene expression microarray analysis of PBMCs from RRMS patients that participated in the ALLEGRO trial.

2. Methods

Peripheral blood samples were obtained from RRMS patients treated with LAQ 0.6 mg/day or placebo as an ancillary study to the Assessment of Oral Laquinimod in Preventing Progression in Multiple Sclerosis trial (Filippi et al., 2014). Blood samples were obtained at baseline and after one and six months of treatment.

2.1. RNA isolation and hybridization

PBMC were extracted from 15 ml peripheral blood, separated by Ficoll–Hypaque gradient. Total RNA was extracted using both Trizol including a DNase digestion step. RNA integrity was assessed by RNA Experion automated electrophoresis system. Probe synthesis using 3 μg total RNA, hybridization, detection, and scanning was performed according to the standard Affymetrix, Inc. USA protocols; cDNA was synthesized using the Two-Cycle cDNA Synthesis Kit (Affymetrix, Inc., USA), and in-vitro transcription performed with the GeneChip IVT Labeling Kit (Affymetrix, Inc., USA). The biotin-labeled IVT–RNA was hybridized to HG-U133A-2 arrays (Affymetrix, Inc., USA) containing 14,500 well-annotated human genes, washed in a GeneChip

Fluidics Station 450 and scanned according to the manufacturer's protocol using GeneArray-TM scanner G2500A (Hewlett Packard, USA).

2.2. Data analysis

Data analysis was performed using Partek Genomics Solution software (www.partek.com). Expression values were computed from raw CEL files by applying the Robust Multi-Chip Average (RMA) background correction algorithm. RMA correction included: 1) values background correction; 2) quintile normalization; 3) log2 transformation; and 4) median polish summarization. ANOVA analysis was applied to compare PBMC gene expression after one and six months of LAQ/placebo treatment as compared with baseline. Age, gender and batch effects were regarded as confounders in the ANOVA model. Genes that significantly changed in the placebo treated patients as compared to baseline were excluded from further analysis to yield only genes exclusively associated with LAQ effects. MIGs were defined as those that differentiated between groups with $p<0.01$. Gene functional annotation, enrichment and pathway analyses to identify the involved biological pathways were performed by Ingenuity Pathways Analysis software (www.ingenuity.com). All p values were applied for multiple testing corrections using False Discovery Rate (FDR) method with a cut off at $p=0.05$.

2.3. Verification by Western blot

Protein fractions were purified from PBMC of 5 patients at baseline and after six months of LAQ treatment. Proteins were extracted from TRIZOL fractions and solubilized following the method reported by Hummon et al., 2007 (Hummon et al., 2007). Equal amounts of proteins were resolved on 10% SDS—PAGE and transferred onto nitrocellulose membranes (Invitrogen kit) for subsequent immune-blotting with antibodies specific for TGFb, ITGB1, CXCR1 and alpha Tubulin (Santa Cruz Biotechnology, Inc Santa Cruz, CA, USA). Blots were analyzed by standard chemi-luminescence (Supersignal Kit, Pierce, Rockford, IL, USA) and visualization was done by ChemiDoc™ XRS System (Bio-Rad).

3. Results

Samples were obtained from 25 RRMS patients, age 38.0±2.0 years, female/male ratio 16/9. The LAQ treatment arm consists of 13 patients, female/male ratio 8/5, age 38.8±2.3 years and the placebo arm consists of 12 patients, female/male ratio 8/4, age 37.2±3.4 years.

LAQ induced a differential gene expression of 354 MIGs after one month of treatment and the number of MIGs increased to 1562 after six months (Table 6 and 7).

The majority of genes that significantly changed expression under LAQ treatment at one and six months of treatment were down regulated (98% and 99 %, respectively).

3. 1. Biological pathways associated with LAQ treatment: down-regulation of TGFb and NFkB signaling and pro inflammatory cytokines

Functional enrichment analysis of 354 MIGs after one month of LAQ treatment disclosed the suppression of molecules associated with different mechanisms of inflammatory response and cellular movement presented in Table 5. Indeed, analysis of the 1562 MIGs after six months showed growing number of genes involved with these mechanisms. Of the significantly suppressed pathways, the TGFb superfamily signaling (Table 5, $p=3.2*10^{-3}$) was suppressed after one as well as after six months of LAQ treatment ($p=4.32*10^{-2}$).

Table 5. Major biological pathways and functions affected by LAQ treatment

After one month of treatment n=345				After six months of treatment n=1562			
Function	Pathway	No. of genes	p-value	Function	Pathway	No. of genes	p-value
Inflammatory response	TGFb signaling	10	$3.2x10^{-3}$	Inflammatory response	TGFb signaling	14	$4.3x10^{-2}$
					IL-12 signaling	11	$3.2x10^{-3}$
Cellular movement	Adhesion & migration of phagocytes	9	$1.2x10^{-3}$	Cellular movement	Invasion of cells	120	$5.6x10^{-5}$
	Chemotaxis of Neutrophils	4	$6.0x10^{-3}$		Adhesion of cells	119	$2.4x10^{-5}$
	Transmigration of leukocytes	8	$1.9x10^{-3}$		Leukocyte extravasation signaling	29	$9.4x10^{-3}$

Downregulation of the TGFb signaling pathway after one month of LAQ treatment was evident by suppression of TGFb and LTBP1 genes, the latter regulates secretion and activation of TGFb and thus promoting a feedback mechanism. After six months, down-regulation of additional TGFb superfamily related genes like BMP2/4/7, MIS, Type II BMP receptor, Smad14/5/6/8, TCF20, TCF2, Runx2 and the downstream ITGB1 was demonstrated (Fig. 9B).

Also, LAQ induced down-regulation of LFA-1 and VLA-4 expression that act with ITGB1 in adhesion of immune cells. The suppression of TGFb pathway after six months of LAQ treatment was accompanied by down regulation of IL-12 signaling pathway ($p=6.2*10^{-3}$) and a wide range of other pro-inflammatory cytokines such as IL-9/11/12/20/36, TNFRSF11A/B, IFNA4/8/10/17, and also the receptors for IL-5/13/20/22 ($p = 3*10^{-3}$ to $9*10^{-3}$).

The molecular signature of LAQ after 6 months was also characterized by suppression of NFkB signaling as demonstrated by down regulation of members of the NFkB signaling that play a role in inflammation including IL-1, IL-1R and IKKg (Fig. 9B).

Altogether, these findings figure out a comprehensive suppression of pro-inflammatory cytokines and the key TGFb and NFkB pathways following six months of LAQ treatment. In view of the early down-regulation of TGFb at one month that precede the down-regulation of genes of pro-inflammatory cytokines, the inventors suggest that TGFb signaling precedes the suppression of inflammatory cytokines and that LAQ down regulates cytokine expression via suppression of TGFb.

Only five LAQ responsive MIGs were upregulated with the common three genes SASH1, FUCA1 and XYLT1 at one and six months. Although none of them integrated in firmed canonical pathway, overexpression of SASH1 and FUCA1 is associated with the inhibition of growth, proliferation, and invasion of cells (Meng et al., 2013).

3. 2. LAQ down-regulates expression of migration, adhesion and leukocyte extravasations genes

Differential expression of cellular movement and migration were observed already after one month of LAQ treatment ($p=3.49*10^{-4}$). These included down-regulation of genes associated with adhesion and migration of phagocytes ($p=1.2*10^{-3}$), chemotaxis of neutrophils ($p=6*10^{-3}$) and transmigration of leukocytes ($p=1.9*10^{-3}$). Genes associated with cell movement and suppressed by LAQ were P selectin that is involved in the initial stage of adhesion and the integrin family members like ITGB1/3/5/6/8 and ITGA8 involved in later steps of adhesion and locomotion during leukocytes extravasation (p-value $1.72*10^{-3}$ to $5.5*10^{-3}$).

The suppressing effects of LAQ on cell adhesion and integrin expression were further enhanced after six months of treatment as was evident by down regulation of genes associated with cellular movement mechanisms (p value $3.15*10^{-6}$ to $3.79*10^{-3}$) including cell invasion ($p=5.6*10^{-5}$), adhesion ($p=2.4*10^{-5}$) and leukocyte extravasation ($p=9.4*10^{-3}$), (Table 5, *supra*).

Similar to the observed effects of suppressed expression of the integrin family members after one month of treatment, suppression was even more evident after six months of LAQ treatment

including integrin genes like ITGB/5/6/8, ITGA8, ITGB8, and ITGA2B (p value $9.84*10^{-4}$ to $1.1*10^{-3}$). In addition, suppression of inflammatory related chemokines like CCL19 and chemokine receptor CXCR1/2 was also demonstrated ($p=6.79*10^{-3}$). Moreover, LAQ down-regulated a range of metalloproteinase family members such as MMP16/24/26/28, and ADAM12/18/22 that play a role during extravasation ($p =4.95*10^{-4}$ to $1.26*10^{-3}$).

3. 3. Verification of key genes associated with LAQ induced molecular pathways

The verification experiments performed by Western Blot analysis show significant down-regulation of key genes associated with most significantly affected biological mechanisms of LAQ. The TGFb protein following six months of LAQ treatment was suppressed by 69.0 % ($p=0.009$) as could be seen from quantification of bands intensities (Fig. 10A). Accordingly, Fig 10B shows down regulation of ITGB1, a common subunit of different integrin receptors by 40 % ($p=0.03$) and of CXCR1 by 24.7 % ($p=0.014$) (Fig. 10C).

4. Discussion

The results demonstrate that the most significant effect of LAQ is induction of suppression of inflammatory response via TGFb and NFkB pathways, as well as decrease in cell movement processes including adhesion, migration and leukocyte extravasation.

The inventors observed down-regulation of signaling pathways involving integrins, chemokines and metalloproteinases accompanied by repression of pro-inflammatory cytokines. These effects were observed in RRMS patients treated over six months-period as compared with baseline. Notably, the suppressive effects of LAQ are already detected as early as one month after initiation of treatment although to a lesser extent, suggesting a time-dependent treatment effect.

The pivotal function of TGFb in the immune system is anti-inflammatory, to maintain tolerance via regulation of lymphocyte proliferation, differentiation and survival. However, in MS it has been shown that in addition to its anti-inflammatory role, TGFb paradoxically can act as pro-inflammatory factor involved in the genesis of the pathogenic EAE-inducing TH17 cells. Thus, deletion of the TGFb gene from activated T cells, is known to abrogate Th17 cell differentiation, resulting in almost complete protection from EAE, confirming TGFb proinflammatory potential (Oh and Li, 2013). In the same process of events, TGFb is involved in stimulation of inflammatory cells adhesion, migration and extravasation, and could promote penetration of auto-aggressive lymphocytes to the central nervous system (CNS) (Bartolome et al., 2003; Brill et al., 2001). TGFb is also known to regulate the expression of IL-9 (Takami et al., 2012) and IL-22 (Sanjabi et al., 2009), thereby enhancing the expression of molecules associated with inflammation. TGFb

itself can be activated by IL-1 (Luo et al., 2009), however IL-1 was also found to be suppressed in LAQ gene expression signature.

In accordance with observations linking TGFb with inflammatory process, the suppression of TGFb and members of the TGFb pathway by LAQ could result in beneficial reduction of active inflammation in MS. The suppression of TGFb signaling by LAQ corroborates with previous publications in which LAQ suppresses MAP3K7 (TAK1) that is strong positive regulator of cellular proliferation mediated by TGFb activation in CD14+ cells (Gurevich et al., 2010; Wan et al., 2006).

The inventors have demonstrated the suppressed expression of large number of cell adhesion and cell movement molecules involved in different stages of leukocytes extravasation under LAQ treatment. The ability of inflammatory cells to move from the periphery to the CNS is a crucial multistep process in MS with the following components down regulated by LAQ: a) Selectin P and IL-8R (CXCR1/2), that mediate rolling and the initial leukocyte-endothelial interactions; b) VLA-4, LFA-1, ITGA2/8, and ITGB1-6 integrins that mediate leukocyte adhesion and transmigration; c) chemokines and chemokine receptors for integrin activation like CCL19 that is responsible for leukocyte arrest and transmigration, and IL-8 receptor (CXCR1/2). These genes are well fitted with the steps of rolling, activation, adhesion, locomotion protrusion and transmigration of immune cells during extravasation to the CNS (as shown in Fig. 8C). Taken together, findings of the present study suggest that LAQ acts through inhibition of immune cells movement, adhesion and transmigration, thereby reducing the migratory capacity of active inflammatory cells trough the blood brain barrier (BBB). The supression of these cell migration functions corroborate with previously reported effects of LAQ- to induce down regulation of various cytokines and integrins such as IL-12, IL-13, IL-17, IFN-γ,TNF-α and VLA-4-mediated adhesiveness resulting in interference with migratory capacity of T cells in EAE (Brück and Wegner, 2011; Jadidi-Niaragh et al., 2011; Wegner et al., 2010).

Similarly, in MS patients, the inventors have demonstrated that LAQ down-regulates IL-1, IL-1R, IL12 and IKKg genes associated with pro-inflammatory NFkB pathway. The suppression of NFkB mechanism by LAQ was also demonstrated in an in-vitro study on PBMC obtained from MS patients (Gurevich et al., 2010) and in astrocytes following LAQ treatment in cuprizone-induced demyelination model (Bruck et al., 2012). NFkB signaling mediates IL-12 activation in macrophages (Murphy et al., 1995). The inventors have determined that LAQ may suppress both IL1 and IL12 dependent inflammation via down regulation of NFkB signaling.

These inflammation counteracting effects of LAQ could be the molecular basis of the positive imaging effect of LAQ in the ALLEGRO trial (Comi et al., 2012; Filippi et al., 2014).

Only 5 genes were up-regulated by LAQ; three of these up regulated genes were up-regulated already after one month of treatment with sustained effect at 6 months; Sash1 and FUCA1 are involved in suppression of proliferation while XYLT catalyzes the biosynthesis of glycosaminoglycan and its high activity was reported in patients with impaired BBB (Ponighaus et al., 2007). After six months of treatment, another growth inhibitor gene PID1 was overexpressed, confirming the suppression of proliferation of CD8+ cells by LAQ (Gurevich et al., 2010).

The inventors believe this to be the first study that characterizes LAQ induced transcriptional profile of RRMS patients demonstrating LAQ suppression of inflammatory cytokines and leukocytes extravasation either directly or via suppression of TGFb superfamily and NFkB signaling, thereby contributing to amelioration of the disease process of MS.

Table 6

Column ID	Gene Symbol	Gene Title	p-value(1.0 vs. 0.0)	Fold-Change (1.0 vs. 0.0)
202380_s_at	NKTR	natural killer-tumor recognition sequence	3.20E-05	-1.12256
215673_at	TEF	thyrotrophic embryonic factor	4.00E-05	-1.16076
219414_at	CLSTN2	calsyntenin 2	4.51E-05	-1.12845
220099_s_at	LUC7L2	LUC7-like 2 (S. cerevisiae)	9.60E-05	-1.15527
215492_x_at	PTCRA	pre T-cell antigen receptor alpha	0.000172567	-1.52614
207426_s_at	TNFSF4	tumor necrosis factor (ligand) superfamily, member 4	0.000172751	-1.7061
205030_at	FABP7	fatty acid binding protein 7, brain	0.000176697	-1.17613
220205_at	TPTE	transmembrane phosphatase with tensin homology	0.000181472	-1.15822

208782_at	FSTL1	follistatin-like 1	0.00019072	-1.69352
201071_x_at	SF3B1	splicing factor 3b, subunit 1, 155kDa	0.000259586	-1.0879
207198_s_at	LIMS1	LIM and senescent cell antigen-like domains 1	0.000294426	-1.44487
206757_at	PDE5A	phosphodiesterase 5A, cGMP-specific	0.000306957	-1.213
209045_at	XPNPEP1	X-prolyl aminopeptidase (aminopeptidase P) 1, soluble	0.000348404	-1.19661
48031_r_at	C5orf4	chromosome 5 open reading frame 4	0.000363815	-1.51923
220921_at	SPANXB1 /// SPANXB2 /// SPANXF1	SPANX family, member B1 /// SPANX family, member B2 /// SPANX family, member F1	0.000369349	-1.16871
202729_s_at	LTBP1	latent transforming growth factor beta binding protein 1	0.000383136	-1.71014
213953_at	KRT20	keratin 20	0.000398517	-1.13707
214146_s_at	PPBP	pro-platelet basic protein (chemokine (C-X-C motif) ligand 7)	0.000468646	-1.45959
214013_s_at	TBC1D1	TBC1 (tre-2/USP6, BUB2, cdc16) domain family, member 1	0.000514065	-1.21818
219388_at	GRHL2	grainyhead-like 2 (Drosophila)	0.000551908	-1.13133
220751_s_at	C5orf4	chromosome 5 open reading frame 4	0.000640518	-1.96738
211252_x_at	PTCRA	pre T-cell antigen receptor alpha	0.000650924	-1.38911
206390_x_at	PF4	platelet factor 4	0.00069054	-1.76355
213666_at	SEPT6	septin 6	0.000693884	-1.13383

212942_s_at	KIAA1199	KIAA1199	0.000714369	-1.12102
203016_s_at	SSX2IP	synovial sarcoma, X breakpoint 2 interacting protein	0.000739497	-1.36137
206116_s_at	TPM1	tropomyosin 1 (alpha)	0.00075228	-1.49626
221556_at	CDC14B	CDC14 cell division cycle 14 homolog B (S. cerevisiae)	0.000762595	-1.48795
221518_s_at	USP47	ubiquitin specific peptidase 47	0.000785063	-1.07574
205612_at	MMRN1	multimerin 1	0.000786871	-1.37634
202468_s_at	CTNNAL1	catenin (cadherin-associated protein), alpha-like 1	0.000828338	-1.41611
210357_s_at	SMOX	spermine oxidase	0.000848049	-1.40727
207206_s_at	ALOX12	arachidonate 12-lipoxygenase	0.000911895	-1.83581
210661_at	GLRA3	glycine receptor, alpha 3	0.000946566	-1.15569
209301_at	CA2	carbonic anhydrase II	0.000964786	-1.68995
211555_s_at	GUCY1B3	guanylate cyclase 1, soluble, beta 3	0.00100045	-1.61803
207934_at	RFPL1	ret finger protein-like 1	0.00102558	-1.14458
220496_at	CLEC1B	C-type lectin domain family 1, member B	0.00102643	-2.04495
204115_at	GNG11	guanine nucleotide binding protein (G protein), gamma 11	0.00102931	-1.67885
220558_x_at	TSPAN32	tetraspanin 32	0.00108103	-1.15615
204319_s_at	RGS10	regulator of G-protein signaling 10	0.00108604	-1.27188
201615_x_at	CALD1	caldesmon 1	0.00112603	-1.44221
203680_at	PRKAR2B	protein kinase, cAMP-dependent, regulatory, type II, beta	0.00119671	-1.87579

206153_at	CYP4F11	cytochrome P450, family 4, subfamily F, polypeptide 11	0.00121638	-1.09486
220810_at	CLCA3P	chloride channel accessory 3 (pseudogene)	0.00123986	-1.14123
40020_at	CELSR3	cadherin, EGF LAG seven-pass G-type receptor 3 (flamingo homolog, Drosophila)	0.00127162	-1.12078
208022_s_at	CDC14B	CDC14 cell division cycle 14 homolog B (S. cerevisiae)	0.00133236	-1.4133
210987_x_at	TPM1	tropomyosin 1 (alpha)	0.00135846	-1.44653
214298_x_at	SEPT6	septin 6	0.00137756	-1.13328
207119_at	PRKG1	protein kinase, cGMP-dependent, type I	0.00141929	-1.18474
210734_x_at	MAX	MYC associated factor X	0.00142961	-1.28358
209689_at	CCDC93	coiled-coil domain containing 93	0.0014704	-1.13336
214749_s_at	ARMCX6 /// LOC653354	armadillo repeat containing, X-linked 6 /// similar to armadillo repeat containi	0.00149785	-1.17832
214023_x_at	TUBB2B	tubulin, beta 2B	0.00153776	-1.15934
208583_x_at	HIST1H2AJ	histone cluster 1, H2aj	0.00154449	-1.27798
205442_at	MFAP3L	microfibrillar-associated protein 3-like	0.0015663	-1.85392
212687_at	LIMS1	LIM and senescent cell antigen-like domains 1	0.00160765	-1.3332
211871_x_at	GNB5	guanine nucleotide binding protein (G protein), beta 5	0.00163175	-1.15867

204793_at	GPRASP1	G protein-coupled receptor associated sorting protein 1	0.00165477	-1.16021
201680_x_at	SRRT	serrate RNA effector molecule homolog (Arabidopsis)	0.00172271	-1.11791
211837_s_at	PTCRA	pre T-cell antigen receptor alpha	0.00177798	-1.27392
219476_at	C1orf116	chromosome 1 open reading frame 116	0.00181581	-1.22156
201178_at	FBXO7	F-box protein 7	0.00186196	-1.13506
203966_s_at	PPM1A	protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform	0.00188506	-1.18222
203817_at	GUCY1B3	guanylate cyclase 1, soluble, beta 3	0.00189066	-1.72974
201125_s_at	ITGB5	integrin, beta 5	0.00191776	-1.71341
201905_s_at	CTDSPL	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatas	0.00197783	-1.46779
200780_x_at	GNAS	GNAS complex locus	0.00198667	-1.15838
203819_s_at	IGF2BP3	insulin-like growth factor 2 mRNA binding protein 3	0.0019919	-1.71954
210986_s_at	TPM1	tropomyosin 1 (alpha)	0.00199934	-1.55544
209806_at	HIST1H2BK	histone cluster 1, H2bk	0.00202655	-1.41838
210684_s_at	DLG4	discs, large homolog 4 (Drosophila)	0.00202851	-1.18659
222157_s_at	WDR48	WD repeat domain 48	0.00207579	-1.10297
212077_at	CALD1	caldesmon 1	0.00217742	-1.89576
214839_at	LOC157627	hypothetical	0.00223956	1.32598

		LOC157627		
207124_s_at	GNB5	guanine nucleotide binding protein (G protein), beta 5	0.00230176	-1.1663
205514_at	ZNF415	zinc finger protein 415	0.00231529	-1.15423
206049_at	SELP	selectin P (granule membrane protein 140kDa, antigen CD62)	0.00232343	-1.64193
206414_s_at	ASAP2	ArfGAP with SH3 domain, ankyrin repeat and PH domain 2	0.00233503	-1.77303
218613_at	PSD3	pleckstrin and Sec7 domain containing 3	0.00234479	-1.25828
200981_x_at	GNAS	GNAS complex locus	0.00238211	-1.1585
211945_s_at	ITGB1	integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes	0.00241794	-1.17026
219926_at	POPDC3	popeye domain containing 3	0.00243065	-1.1575
204081_at	NRGN	neurogranin (protein kinase C substrate, RC3)	0.00243424	-1.60366
205730_s_at	ABLIM3	actin binding LIM protein family, member 3	0.00246133	-1.54178
213725_x_at	XYLT1	xylosyltransferase I	0.00253677	1.31402
210702_s_at	PTGIS	prostaglandin I2 (prostacyclin) synthase	0.00258067	-1.09522
215139_at	ARHGEF10	Rho guanine nucleotide exchange factor (GEF) 10	0.00258297	-1.17563
205463_s_at	PDGFA	platelet-derived growth factor alpha polypeptide	0.00261003	-1.53627

204628_s_at	ITGB3	integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)	0.00264187	-1.57906
201121_s_at	PGRMC1	progesterone receptor membrane component 1	0.00266076	-1.44314
215071_s_at	HIST1H2AC	histone cluster 1, H2ac	0.00271978	-1.62836
212273_x_at	GNAS	GNAS complex locus	0.00273624	-1.15606
204482_at	CLDN5	claudin 5	0.00276964	-1.36386
210493_s_at	MFAP3L	microfibrillar-associated protein 3-like	0.0027754	-1.46358
201120_s_at	PGRMC1	progesterone receptor membrane component 1	0.0027801	-1.43219
202423_at	MYST3	MYST histone acetyltransferase (monocytic leukemia) 3	0.00280673	-1.07974
200722_s_at	CAPRIN1	cell cycle associated protein 1	0.00288696	-1.15665
201617_x_at	CALD1	caldesmon 1	0.0028931	-1.32568
218751_s_at	FBXW7	F-box and WD repeat domain containing 7	0.00289921	-1.11226
209839_at	DNM3	dynamin 3	0.00294256	-1.79997
211190_x_at	CD84	CD84 molecule	0.0029693	-1.16616
202127_at	PRPF4B	PRP4 pre-mRNA processing factor 4 homolog B (yeast)	0.00299632	-1.13501
202280_at	---	---	0.00302852	-1.15673
212031_at	RBM25	RNA binding motif protein 25	0.00302972	-1.10451
204042_at	WASF3	WAS protein family, member 3	0.00304453	-1.60611
208406_s_at	GRAP2	GRB2-related adaptor protein 2	0.0030481	-1.39443
200665_s_at	SPARC	secreted protein, acidic, cysteine-rich	0.00304843	-1.77594

		(osteonectin)		
206283_s_at	TAL1	T-cell acute lymphocytic leukemia 1	0.00307052	-1.75245
218407_x_at	NENF	neuron derived neurotrophic factor	0.0030954	-1.14125
206698_at	XK	X-linked Kx blood group (McLeod syndrome)	0.00309645	-1.88028
207389_at	GP1BA	glycoprotein Ib (platelet), alpha polypeptide	0.00310255	-1.54848
215240_at	ITGB3	integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)	0.00313548	-1.58871
217456_x_at	HLA-E	major histocompatibility complex, class I, E	0.00314152	-1.06184
207421_at	CA5A	carbonic anhydrase VA, mitochondrial	0.00315794	-1.24281
220037_s_at	LYVE1	lymphatic vessel endothelial hyaluronan receptor 1	0.00316412	-1.13941
203085_s_at	TGFB1	transforming growth factor, beta 1	0.00316654	-1.24041
201736_s_at	MARCH6	membrane-associated ring finger (C3HC4) 6	0.00323685	-1.13929
206964_at	NAT8B	N-acetyltransferase 8B (GCN5-related, putative, gene/pseudogene)	0.00333385	-1.74593
215047_at	TRIM58	tripartite motif-containing 58	0.00338565	-1.77665
211421_s_at	RET	ret proto-oncogene	0.00341726	-1.22099
218711_s_at	SDPR	serum deprivation response (phosphatidylserine	0.00342263	-1.66157

		binding protein)		
336_at	TBXA2R	thromboxane A2 receptor	0.00343156	-1.43266
200929_at	TMED10	transmembrane emp24-like trafficking protein 10 (yeast)	0.00344518	-1.09881
209871_s_at	APBA2	amyloid beta (A4) precursor protein-binding, family A, member 2	0.00349415	-1.16326
201058_s_at	MYL9	myosin, light chain 9, regulatory	0.003504	-1.74013
207846_at	POU1F1	POU class 1 homeobox 1	0.00351318	-1.09086
208579_x_at	H2BFS /// HIST1H2BK	H2B histone family, member S /// histone cluster 1, H2bk	0.00351435	-1.48066
220759_at	FAM12B	family with sequence similarity 12, member B (epididymal)	0.0035357	-1.1468
200931_s_at	VCL	vinculin	0.00355492	-1.40602
217595_at	GSPT1	G1 to S phase transition 1	0.00359115	-1.11645
204704_s_at	ALDOB	aldolase B, fructose-bisphosphate	0.00362444	-1.11912
207856_s_at	LOC150776 /// SMPD4	sphingomyelin phosphodiesterase 4, neutral membrane pseudogene /// sphingomyelin	0.00363765	-1.0672
218928_s_at	SLC37A1	solute carrier family 37 (glycerol-3-phosphate transporter), member 1	0.00364173	-1.12611

212667_at	SPARC	secreted protein, acidic, cysteine-rich (osteonectin)	0.00365945	-1.72956
214548_x_at	GNAS	GNAS complex locus	0.00366147	-1.15948
221392_at	TAS2R4	taste receptor, type 2, member 4	0.00366806	-1.20308
200622_x_at	CALM3	calmodulin 3 (phosphorylase kinase, delta)	0.00368294	-1.2967
212178_s_at	POM121 /// POM121C	POM121 membrane glycoprotein (rat) /// POM121 membrane glycoprotein C	0.00369813	-1.09132
215993_at	---	---	0.00369964	-1.07521
215655_at	GRIK2	Glutamate receptor, ionotropic, kainate 2	0.00371565	-1.12171
218468_s_at	GREM1	gremlin 1, cysteine knot superfamily, homolog (Xenopus laevis)	0.00374196	-1.11604
205388_at	TNNC2	troponin C type 2 (fast)	0.00376489	-1.21183
207750_at	EPS15L2	epidermal growth factor receptor pathway substrate 15-like 2	0.00376694	-1.1441
212573_at	ENDOD1	endonuclease domain containing 1	0.00376788	-1.29339
210270_at	RGS6	regulator of G-protein signaling 6	0.00377039	-1.25086
211185_s_at	SF3B1	splicing factor 3b, subunit 1, 155kDa	0.00378516	-1.0809
205347_s_at	TMSB15A	thymosin beta 15a	0.0038153	-1.11916
205383_s_at	ZBTB20	zinc finger and BTB domain containing 20	0.00387924	-1.13702
214046_at	FUT9	fucosyltransferase 9 (alpha (1,3)	0.00390947	-1.12688

		fucosyltransferase)		
212062_at	ATP9A	ATPase, class II, type 9A	0.00394326	-1.44071
214974_x_at	CXCL5	chemokine (C-X-C motif) ligand 5	0.00401473	-1.73103
209331_s_at	MAX	MYC associated factor X	0.00402443	-1.24493
215306_at	---	---	0.00405048	-1.22628
214542_x_at	HIST1H2AI	histone cluster 1, H2ai	0.0040542	-1.2842
211948_x_at	BAT2D1	BAT2 domain containing 1	0.00405795	-1.08274
202123_s_at	ABL1	c-abl oncogene 1, receptor tyrosine kinase	0.00406538	-1.10234
211546_x_at	SNCA	synuclein, alpha (non A4 component of amyloid precursor)	0.00409573	-1.35092
208501_at	GFI1B	growth factor independent 1B transcription repressor	0.00411391	-1.55771
200661_at	CTSA	cathepsin A	0.00411941	-1.29244
215820_x_at	SNX13	sorting nexin 13	0.00412146	-1.18742
204486_at	---	---	0.00413941	-1.18519
201529_s_at	RPA1	replication protein A1, 70kDa	0.00422086	-1.26569
214752_x_at	FLNA	filamin A, alpha	0.00426746	-1.14045
208453_s_at	XPNPEP1	X-prolyl aminopeptidase (aminopeptidase P) 1, soluble	0.00430113	-1.19059
203086_at	KIF2A	kinesin heavy chain member 2A	0.00434355	-1.27703
214631_at	ZBTB33	zinc finger and BTB domain containing 33	0.0043722	-1.13452
202728_s_at	LTBP1	latent transforming	0.00437355	-1.47988

		growth factor beta binding protein 1		
208776_at	PSMD11	proteasome (prosome, macropain) 26S subunit, non-ATPase, 11	0.00439519	-1.12238
212751_at	UBE2N	ubiquitin-conjugating enzyme E2N (UBC13 homolog, yeast)	0.00441391	-1.10218
204437_s_at	FOLR1	folate receptor 1 (adult)	0.0044397	-1.21956
215111_s_at	TSC22D1	TSC22 domain family, member 1	0.00446803	-1.61432
217816_s_at	PCNP	PEST proteolytic signal containing nuclear protein	0.00447658	-1.13528
205165_at	CELSR3	cadherin, EGF LAG seven-pass G-type receptor 3 (flamingo homolog, Drosophila)	0.00452773	-1.16533
206465_at	ACSBG1	acyl-CoA synthetase bubblegum family member 1	0.004567	-1.54878
208924_at	RNF11	ring finger protein 11	0.00458077	-1.38056
206941_x_at	SEMA3E	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphor	0.00459381	-1.14106
210075_at	MARCH2	membrane-associated ring finger (C3HC4) 2	0.00459416	-1.3917
220186_s_at	PCDH24	protocadherin 24	0.00460173	-1.12071
201480_s_at	SUPT5H	suppressor of Ty 5 homolog (S. cerevisiae)	0.00461915	-1.10301
200904_at	HLA-E	major histocompatibility complex, class I, E	0.00463895	-1.12592
206254_at	EGF	epidermal growth factor	0.00468322	-1.73397

		(beta-urogastrone)		
214459_x_at	HLA-C	major histocompatibility complex, class I, C	0.00473524	-1.06284
200859_x_at	FLNA	filamin A, alpha	0.00474228	-1.15462
201938_at	CDK2AP1	cyclin-dependent kinase 2 associated protein 1	0.0047647	-1.36598
202378_s_at	LEPROT	leptin receptor overlapping transcript	0.00479261	-1.26088
219710_at	SH3TC2	SH3 domain and tetratricopeptide repeats 2	0.00480083	-1.22839
212242_at	TUBA4A	tubulin, alpha 4a	0.00489677	-1.25565
213511_s_at	MTMR1	myotubularin related protein 1	0.004902	-1.09827
220109_at	TF	transferrin	0.00492572	-1.12186
217705_at	PRKD1	protein kinase D1	0.00494361	-1.08153
208753_s_at	NAP1L1	nucleosome assembly protein 1-like 1	0.00495688	-1.22128
201280_s_at	DAB2	disabled homolog 2, mitogen-responsive phosphoprotein (Drosophila)	0.00497063	-1.64395
202838_at	FUCA1	fucosidase, alpha-L- 1, tissue	0.00499711	1.56419
205426_s_at	HIP1	huntingtin interacting protein 1	0.00499868	-1.14213
211154_at	THPO	thrombopoietin	0.00502652	-1.11697
214577_at	MAP1B	microtubule-associated protein 1B	0.00512459	-1.14783
37966_at	PARVB	parvin, beta	0.00513617	-1.45109
209767_s_at	GP1BB /// SEPT5	glycoprotein Ib (platelet), beta polypeptide /// septin 5	0.00515773	-1.47137

40687_at	GJA4	gap junction protein, alpha 4, 37kDa	0.00516689	-1.14585
216463_at	---	---	0.00517514	-1.14524
205128_x_at	PTGS1	prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxyge	0.00517864	-1.54268
221942_s_at	GUCY1A3	guanylate cyclase 1, soluble, alpha 3	0.00526751	-1.70831
207156_at	HIST1H2AG	histone cluster 1, H2ag	0.0053042	-1.67358
211858_x_at	GNAS	GNAS complex locus	0.00533874	-1.13613
212692_s_at	LRBA	LPS-responsive vesicle trafficking, beach and anchor containing	0.00540408	-1.1862
211728_s_at	HYAL3	hyaluronoglucosaminidase 3	0.00545859	-1.16784
220336_s_at	GP6	glycoprotein VI (platelet)	0.00546958	-1.61325
217083_at	IGHG1	Immunoglobulin heavy constant gamma 1 (G1m marker)	0.00548613	-1.16387
208327_at	CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13	0.00550711	-1.14862
221555_x_at	CDC14B	CDC14 cell division cycle 14 homolog B (S. cerevisiae)	0.0055286	-1.35261
211567_at	---	---	0.00553946	-1.12571
208403_x_at	MAX	MYC associated factor X	0.00557349	-1.29399
208989_s_at	KDM2A	lysine (K)-specific demethylase 2A	0.00557809	-1.10556
201616_s_at	CALD1	caldesmon 1	0.00558092	-1.48431

204993_at	GNAZ	guanine nucleotide binding protein (G protein), alpha z polypeptide	0.00558421	-1.47787
221764_at	C19orf22	chromosome 19 open reading frame 22	0.00558498	-1.1412
206167_s_at	ARHGAP6	Rho GTPase activating protein 6	0.0055881	-1.76822
204627_s_at	ITGB3	integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)	0.00559095	-1.9911
200885_at	RHOC	ras homolog gene family, member C	0.00563494	-1.28435
218117_at	RBX1	ring-box 1	0.0056402	-1.1728
206655_s_at	GP1BB /// SEPT5	glycoprotein Ib (platelet), beta polypeptide /// septin 5	0.00564505	-1.81428
200844_s_at	PRDX6	peroxiredoxin 6	0.00565286	-1.14511
216881_x_at	PRB4	proline-rich protein BstNI subfamily 4	0.00566372	-1.11675
213746_s_at	FLNA	filamin A, alpha	0.00567458	-1.16364
208490_x_at	HIST1H2BF	histone cluster 1, H2bf	0.00567635	-1.43467
219202_at	RHBDF2	rhomboid 5 homolog 2 (Drosophila)	0.00568725	-1.12168
222382_x_at	NUP205	nucleoporin 205kDa	0.00571901	-1.14196
203998_s_at	SYT1	synaptotagmin I	0.00575584	-1.13457
209826_at	EGFL8 /// PPT2	EGF-like-domain, multiple 8 /// palmitoyl-protein thioesterase 2	0.0058323	-1.1054
208601_s_at	TUBB1	tubulin, beta 1	0.00591408	-1.84224
214958_s_at	TMC6	transmembrane channel-like 6	0.00592428	-1.12494
217335_at	FLJ11292	hypothetical protein FLJ11292	0.00594468	-1.15949

213864_s_at	NAP1L1	nucleosome assembly protein 1-like 1	0.00597059	-1.13884
203180_at	ALDH1A3	aldehyde dehydrogenase 1 family, member A3	0.00600686	-1.16713
202332_at	CSNK1E	casein kinase 1, epsilon	0.00600712	-1.08867
210988_s_at	PRUNE	prune homolog (Drosophila)	0.00603465	-1.30051
216896_at	COL4A3	collagen, type IV, alpha 3 (Goodpasture antigen)	0.00603529	-1.14088
220847_x_at	ZNF221	zinc finger protein 221	0.00606358	1.15477
208931_s_at	ILF3	interleukin enhancer binding factor 3, 90kDa	0.00609592	-1.14798
221160_s_at	CABP5	calcium binding protein 5	0.00612012	-1.56239
201528_at	RPA1	replication protein A1, 70kDa	0.00612054	-1.2309
208750_s_at	ARF1	ADP-ribosylation factor 1	0.00615213	-1.10243
208523_x_at	HIST1H2BI	histone cluster 1, H2bi	0.00617675	-1.47477
215813_s_at	PTGS1	prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxyge	0.00620004	-1.55575
214917_at	PRKAA1	protein kinase, AMP-activated, alpha 1 catalytic subunit	0.00621432	-1.17283
204000_at	GNB5	guanine nucleotide binding protein (G protein), beta 5	0.00623899	-1.19485
207046_at	HIST2H4A /// HIST2H4B	histone cluster 2, H4a /// histone cluster 2, H4b	0.00626313	-1.23715
201885_s_at	CYB5R3	cytochrome b5 reductase 3	0.0062861	-1.15347

221748_s_at	TNS1	tensin 1	0.0062959	-1.4944
216513_at	DCT	dopachrome tautomerase (dopachrome delta-isomerase, tyrosine-related protein 2)	0.00633287	-1.16456
204187_at	GMPR	guanosine monophosphate reductase	0.00636191	-1.47328
220518_at	ABI3BP	ABI family, member 3 (NESH) binding protein	0.00645579	-1.13443
217673_x_at	GNAS	GNAS complex locus	0.00646359	-1.13184
213236_at	SASH1	SAM and SH3 domain containing 1	0.0064869	1.90481
205434_s_at	AAK1	AP2 associated kinase 1	0.00656002	-1.0984
211982_x_at	XPO6	exportin 6	0.00657111	-1.07265
210074_at	CTSL2	cathepsin L2	0.00658045	-1.24334
219705_at	QSER1	glutamine and serine rich 1	0.00662733	-1.17822
208786_s_at	MAP1LC3B	microtubule-associated protein 1 light chain 3 beta	0.00665976	-1.14821
209651_at	TGFB1I1	transforming growth factor beta 1 induced transcript 1	0.00668902	-1.76594
215122_at	TBX6	T-box 6	0.00679541	-1.14526
206110_at	---	---	0.00681334	-1.79605
207745_at	CABP2	calcium binding protein 2	0.00682426	-1.13079
211334_at	MRE11A	MRE11 meiotic recombination 11 homolog A (S. cerevisiae)	0.00687602	-1.12163

202501_at	MAPRE2	microtubule-associated protein, RP/EB family, member 2	0.00688368	-1.12271
204328_at	TMC6	transmembrane channel-like 6	0.00689317	-1.08397
213598_at	---	---	0.00699509	-1.22087
205870_at	BDKRB2	bradykinin receptor B2	0.00701629	-1.14085
211026_s_at	MGLL	monoglyceride lipase	0.00710106	-1.60334
219983_at	HRASLS	HRAS-like suppressor	0.00719792	-1.52976
213908_at	WHAMML1 /// WHAMML2	WAS protein homolog associated with actin, golgi membranes and microtubules-like	0.00719896	-1.37039
208792_s_at	CLU	clusterin	0.00721848	-1.79473
204597_x_at	STC1	stanniocalcin 1	0.00723265	-1.14445
207963_at	C6orf54	chromosome 6 open reading frame 54	0.00723289	-1.15074
213046_at	PABPN1	poly(A) binding protein, nuclear 1	0.00723382	-1.1431
208690_s_at	PDLIM1	PDZ and LIM domain 1	0.00723389	-1.321
208791_at	CLU	clusterin	0.00725265	-1.77614
209423_s_at	PHF20	PHD finger protein 20	0.00725781	-1.14876
221746_at	UBL4A	ubiquitin-like 4A	0.00726803	-1.2092
212742_at	RNF115	ring finger protein 115	0.00727752	-1.09141
205221_at	HGD	homogentisate 1,2-dioxygenase (homogentisate oxidase)	0.00729169	-1.52962
214369_s_at	RASGRP2	RAS guanyl releasing protein 2 (calcium and DAG-regulated)	0.00738935	-1.10618
210183_x_at	PNN	pinin, desmosome associated protein	0.00742741	-1.10331
207799_x_at	---	---	0.00743344	-1.20384

217928_s_at	SAPS3	SAPS domain family, member 3	0.00749046	-1.10225
213431_x_at	SFI1	Sfi1 homolog, spindle assembly associated (yeast)	0.00750358	-1.06935
211059_s_at	GOLGA2	golgi autoantigen, golgin subfamily a, 2	0.00750762	-1.14379
202708_s_at	HIST2H2BE	histone cluster 2, H2be	0.00757968	-1.54991
222121_at	SGEF	Src homology 3 domain-containing guanine nucleotide exchange factor	0.00760512	-1.1164
215653_at	---	---	0.00760953	-1.11511
201124_at	ITGB5	integrin, beta 5	0.0076181	-1.25169
214308_s_at	HGD	homogentisate 1,2-dioxygenase (homogentisate oxidase)	0.00764686	-1.64821
217912_at	DUS1L	dihydrouridine synthase 1-like (S. cerevisiae)	0.00767399	-1.08336
202974_at	MPP1	membrane protein, palmitoylated 1, 55kDa	0.00775127	-1.36968
200905_x_at	HLA-E	major histocompatibility complex, class I, E	0.00775135	-1.07063
216261_at	ITGB3	integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)	0.0077566	-1.37764
206204_at	GRB14	growth factor receptor-bound protein 14	0.00781703	-1.79964
203414_at	MMD	monocyte to macrophage differentiation-associated	0.00782001	-1.41852
219779_at	ZFHX4	zinc finger homeobox 4	0.00782075	-1.16711
202573_at	CSNK1G2	casein kinase 1, gamma	0.00784114	-1.11116

		2		
208527_x_at	HIST1H2BE	histone cluster 1, H2be	0.00788446	-1.41486
213306_at	MPDZ	multiple PDZ domain protein	0.00799342	-1.10219
216231_s_at	B2M	beta-2-microglobulin	0.00809127	-1.05409
207554_x_at	TBXA2R	thromboxane A2 receptor	0.00813716	-1.28702
217963_s_at	NGFRAP1	nerve growth factor receptor (TNFRSF16) associated protein 1	0.00815053	-1.41005
201904_s_at	CTDSPL	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatas	0.00815064	-1.51442
205754_at	F2	coagulation factor II (thrombin)	0.00816234	-1.14373
204466_s_at	SNCA	synuclein, alpha (non A4 component of amyloid precursor)	0.0081789	-1.56209
201029_s_at	CD99	CD99 molecule	0.00820335	-1.12753
202466_at	POLS	polymerase (DNA directed) sigma	0.00822683	-1.10075
207550_at	MPL	myeloproliferative leukemia virus oncogene	0.00828883	-1.89086
208506_at	HIST1H3F	histone cluster 1, H3f	0.0083864	-1.13083
202774_s_at	SFRS8	splicing factor, arginine/serine-rich 8 (suppressor-of-white-apricot homolog, Dr	0.00842382	-1.09754
208343_s_at	NR5A2	nuclear receptor subfamily 5, group A, member 2	0.00845048	-1.11703

202778_s_at	ZMYM2	zinc finger, MYM-type 2	0.00850235	-1.12722
207523_at	C6orf10	chromosome 6 open reading frame 10	0.00859283	-1.11067
219503_s_at	TMEM40	transmembrane protein 40	0.00859971	-1.45661
218704_at	RNF43	ring finger protein 43	0.00873092	-1.14893
209586_s_at	PRUNE	prune homolog (Drosophila)	0.00873312	-1.23705
211449_at	MSH6	mutS homolog 6 (E. coli)	0.00875942	-1.11398
203896_s_at	PLCB4	phospholipase C, beta 4	0.00876295	-1.13939
204629_at	PARVB	parvin, beta	0.00884733	-1.27543
216623_x_at	TOX3	TOX high mobility group box family member 3	0.00885472	-1.09839
204196_x_at	PKNOX1	PBX/knotted 1 homeobox 1	0.00892223	-1.11739
215101_s_at	CXCL5	chemokine (C-X-C motif) ligand 5	0.00893221	-1.66669
218243_at	RUFY1	RUN and FYVE domain containing 1	0.00894778	-1.43684
204467_s_at	SNCA	synuclein, alpha (non A4 component of amyloid precursor)	0.00896008	-1.47629
219857_at	C10orf81	chromosome 10 open reading frame 81	0.00897475	-1.18546
216867_s_at	PDGFA	platelet-derived growth factor alpha polypeptide	0.00897825	-1.3116
206779_s_at	ASMT	acetylserotonin O-methyltransferase	0.00905468	-1.13282
214938_x_at	HMGB1	high-mobility group box 1	0.00906415	-1.08357

220094_s_at	CCDC90A	coiled-coil domain containing 90A	0.00907588	-1.32015
207808_s_at	PROS1	protein S (alpha)	0.00911187	-1.96407
200833_s_at	hCG_1757335 /// RAP1B	RAP1B, member of RAS oncogene family pseudogene /// RAP1B, member of RAS oncogen	0.00912774	-1.12905
206176_at	BMP6	bone morphogenetic protein 6	0.00916216	-1.52992
210360_s_at	MTSS1	metastasis suppressor 1	0.00917743	-1.16565
211522_s_at	GNRHR	gonadotropin-releasing hormone receptor	0.00918361	-1.12079
209840_s_at	LRRN3	leucine rich repeat neuronal 3	0.00922884	1.86067
214514_at	MCM3AP	minichromosome maintenance complex component 3 associated protein	0.00924948	-1.13224
202620_s_at	PLOD2	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	0.00936232	-1.26035
208752_x_at	NAP1L1	nucleosome assembly protein 1-like 1	0.00940735	-1.13425
202619_s_at	PLOD2	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	0.00942205	-1.28918
207397_s_at	HOXD13	homeobox D13	0.00958266	-1.11525
61297_at	CASKIN2	CASK interacting protein 2	0.00961064	-1.11013
213765_at	MFAP5	microfibrillar associated protein 5	0.00964722	-1.09199
207558_s_at	PITX2	paired-like homeodomain 2	0.00964956	-1.10328

207827_x_at	SNCA	synuclein, alpha (non A4 component of amyloid precursor)	0.00976329	-1.35299
202555_s_at	MYLK	myosin light chain kinase	0.00978872	-1.59189
212151_at	PBX1	pre-B-cell leukemia homeobox 1	0.00982704	-1.5597
200845_s_at	PRDX6	peroxiredoxin 6	0.00986511	-1.2308
217736_s_at	EIF2AK1	eukaryotic translation initiation factor 2-alpha kinase 1	0.00989935	-1.23452
213828_x_at	H3F3A /// H3F3B /// LOC440926	H3 histone, family 3A /// H3 histone, family 3B (H3.3B) /// H3 histone, family 3	0.00991103	-1.09735
216625_at	---	---	0.00997586	-1.10058

Table 7

Gene Symbol	Gene Title	p-value(4.0 vs. 0.0)	Fold-Change(4.0 vs. 0.0)
TMEM158	transmembrane protein 158	0.001631	-1.88182
TRIM58	tripartite motif-containing 58	0.004607	-1.73605
FSTL1	follistatin-like 1	0.001763	-1.66003
SNCA	synuclein, alpha (non A4 component of amyloid precursor)	0.006379	-1.59767
ITGB5	Integrin, beta 5	0.00485	-1.5805
TNS1	tensin 1	0.003402	-1.53358

ATP1B1	ATPase, Na+/K+ transporting, beta 1 polypeptide	0.008818	-1.51106
C5orf4	chromosome 5 open reading frame 4	0.005208	-1.46004
LRP12	low density lipoprotein-related protein 12	0.002832	-1.42261
CTNNAL1	catenin (cadherin-associated protein), alpha-like 1	0.009018	-1.40804
GEM	GTP binding protein overexpressed in skeletal muscle	0.002764	-1.40178
KIAA1466	KIAA1466 gene	0.002973	-1.39035
ALDH1A2	aldehyde dehydrogenase 1 family, member A2	0.000677	-1.38981
MAP4K3	mitogen-activated protein kinase kinase kinase kinase 3	0.007221	-1.37714
SNCA	synuclein, alpha (non A4 component of amyloid precursor)	0.007255	-1.37607
RAB6B	RAB6B, member RAS oncogene family	0.007576	-1.37568
PSD3	pleckstrin and Sec7 domain containing 3	0.000178	-1.37423
RIPK2	receptor-interacting serine-threonine kinase 2	0.008392	-1.36879

RAMP3	receptor (G protein-coupled) activity modifying protein 3	0.002203	-1.36845
PTCRA	pre T-cell antigen receptor alpha	0.003563	-1.35879
CALD1	caldesmon 1	0.002914	-1.35604
CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1	0.001334	-1.35372
PSD3	pleckstrin and Sec7 domain containing 3	0.000673	-1.35294
PDLIM7	PDZ and LIM domain 7 (enigma)	0.003532	-1.34658
COBLL1	COBL-like 1	0.002662	-1.34562
FUT3	fucosyltransferase 3 (galactoside 3(4)-L-fucosyltransferase, Lewis blood group)	2.63E-05	-1.34512
SMOX	spermine oxidase	0.006872	-1.34018
TGM2	transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)	0.002055	-1.33815
LRRC50	leucine rich repeat containing 50	0.004871	-1.33114
CST6	cystatin E/M	0.001427	-1.33016
OR7A17	olfactory receptor, family 7, subfamily A, member 17	0.000118	-1.32853

C6orf145	chromosome 6 open reading frame 145	0.00109	-1.32816
DLEU2 /// DLEU2L	deleted in lymphocytic leukemia 2 (non-protein coding) /// deleted in lymphocytic leuke	0.009215	-1.32582
CPT2	carnitine palmitoyltransferase 2	0.002605	-1.32033
HGF	hepatocyte growth factor (hepapoietin A; scatter factor)	0.007517	-1.31941
TNS1	tensin 1	0.002806	-1.31579
SPRY1	sprouty homolog 1, antagonist of FGF signaling (Drosophila)	0.004614	-1.30993
PLOD2	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	0.007309	-1.30719
CD80	CD80 molecule	0.008637	-1.30572
KYNU	kynureninase (L-kynurenine hydrolase)	0.009541	-1.30549
BCAT1	branched chain aminotransferase 1, cytosolic	0.009502	-1.30486
NHLH1	nescient helix loop helix 1	0.00122	-1.30451
AHCTF1	AT hook containing transcription factor 1	0.006984	-1.30418
HOXA10	homeobox A10	0.007051	-1.30259
MTMR3	myotubularin related protein 3	0.001598	-1.30189
---	---	0.000939	-1.30069
VAC14	Vac14 homolog (S. cerevisiae)	2.51E-05	-1.29695

CLCF1	cardiotrophin-like cytokine factor 1	0.003153	-1.2966
FGF5	fibroblast growth factor 5	0.001	-1.29505
TAL1	T-cell acute lymphocytic leukemia 1	0.000808	-1.29347
SAMD14	sterile alpha motif domain containing 14	0.00157	-1.29276
ELL2	elongation factor, RNA polymerase II, 2	0.006259	-1.29209
CHN1	chimerin (chimaerin) 1	0.006634	-1.2914
SLC7A1	solute carrier family 7 (cationic amino acid transporter, y+ system), member 1	0.009963	-1.28978
GRK5	G protein-coupled receptor kinase 5	0.000218	-1.28944
PARD3	par-3 partitioning defective 3 homolog (C. elegans)	0.000992	-1.28781
VPS37B	vacuolar protein sorting 37 homolog B (S. cerevisiae)	0.004355	-1.28765
CYP2B6 /// CYP2B7P1	cytochrome P450, family 2, subfamily B, polypeptide 6 /// cytochrome P450, family 2, su	0.001079	-1.2873
MALL	mal, T-cell differentiation protein-like	0.000476	-1.28554
ALX4	ALX homeobox 4	1.18E-05	-1.28536

SOX15	SRY (sex determining region Y)-box 15	0.000755	-1.28501
KRT5	keratin 5	0.000738	-1.28477
ESPL1	extra spindle pole bodies homolog 1 (S. cerevisiae)	0.003676	-1.28424
STARD8	StAR-related lipid transfer (START) domain containing 8	0.00219	-1.28408
PSD3	pleckstrin and Sec7 domain containing 3	0.003653	-1.28307
KIAA0195	KIAA0195	3.69E-05	-1.28154
MYO9B	myosin IXB	0.000252	-1.27944
HIP1R /// LOC100294412	huntingtin interacting protein 1 related /// similar to KIAA0655 protein	0.006353	-1.2794
EFNB1	ephrin-B1	0.000145	-1.27858
ERN1	endoplasmic reticulum to nucleus signaling 1	0.001593	-1.27656
RHD	Rh blood group, D antigen	0.005698	-1.27635
MFAP3L	microfibrillar-associated protein 3-like	0.002875	-1.27538
PLA1A	phospholipase A1 member A	0.005885	-1.27427
POFUT2	protein O-fucosyltransferase 2	0.004736	-1.27411
C8orf39	chromosome 8 open reading frame 39	0.002547	-1.27348
CRYBB2	crystallin, beta B2	0.000156	-1.27288

CYP4A11	cytochrome P450, family 4, subfamily A, polypeptide 11	0.000381	-1.27285
PVRL2	poliovirus receptor-related 2 (herpesvirus entry mediator B)	0.007308	-1.27216
CLCNKB	chloride channel Kb	0.001537	-1.27136
MRAS	muscle RAS oncogene homolog	0.002321	-1.27101
NFIB	nuclear factor I/B	0.000362	-1.2706
FKSG2	apoptosis inhibitor	0.003687	-1.27027
SLC11A2	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	0.008176	-1.26987
FZR1	fizzy/cell division cycle 20 related 1 (Drosophila)	0.006166	-1.26883
ZNF550	zinc finger protein 550	0.00302	-1.26876
GLP1R	glucagon-like peptide 1 receptor	0.001684	-1.26854
SLC19A1	solute carrier family 19 (folate transporter), member 1	0.003885	-1.26843
RTN2	reticulon 2	0.008304	-1.26775
PAPOLA	poly(A) polymerase alpha	0.009359	-1.2676
STC1	stanniocalcin 1	0.001341	-1.26734
GK	glycerol kinase	0.004541	-1.26678

EXOSC6	exosome component 6	0.00268	-1.26637
---	---	4.96E-05	-1.26602
RAPSN	receptor-associated protein of the synapse	0.003697	-1.26598
HFE	hemochromatosis	0.000648	-1.26583
EHD2	EH-domain containing 2	0.001249	-1.26575
RIOK3	RIO kinase 3 (yeast)	0.004132	-1.26516
UBE2I	Ubiquitin-conjugating enzyme E2I (UBC9 homolog, yeast)	0.00062	-1.26466
C15orf2	chromosome 15 open reading frame 2	0.002573	-1.26354
DMD	dystrophin	0.006011	-1.26327
PRLH	prolactin releasing hormone	0.001657	-1.26177
MAP2K2	Mitogen-activated protein kinase kinase 2	0.001555	-1.26176
TP63	tumor protein p63	0.001463	-1.26066
DACH1	dachshund homolog 1 (Drosophila)	0.002299	-1.26061
PPP5C	protein phosphatase 5, catalytic subunit	0.002092	-1.26051
SLC26A1	solute carrier family 26 (sulfate transporter), member 1	0.000553	-1.26034

NUDT7	nudix (nucleoside diphosphate linked moiety X)-type motif 7	0.004276	-1.25953
KCNJ12	potassium inwardly-rectifying channel, subfamily J, member 12	0.000307	-1.25907
ENTPD7	ectonucleoside triphosphate diphosphohydrolase 7	0.00881	-1.25885
SLC26A1	solute carrier family 26 (sulfate transporter), member 1	0.000894	-1.25847
PRRG3	proline rich Gla (G-carboxyglutamic acid) 3 (transmembrane)	0.001239	-1.25847
RGS6	regulator of G-protein signaling 6	0.007795	-1.25638
ZBED2	zinc finger, BED-type containing 2	0.000482	-1.25597
---	---	1.57E-05	-1.25554
FICD	FIC domain containing	0.005002	-1.25533
ARHGAP1	Rho GTPase activating protein 1	0.002967	-1.25434
ARHGDIA	Rho GDP dissociation inhibitor (GDI) alpha	0.00427	-1.25429
SDHB	succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	0.003554	-1.25315

AMHR2	anti-Mullerian hormone receptor, type II	0.000653	-1.25279
ABCA4	ATP-binding cassette, sub-family A (ABC1), member 4	0.001332	-1.25263
TCF20	transcription factor 20 (AR1)	0.005851	-1.2525
BGN	biglycan	0.00473	-1.25217
CASP7	caspase 7, apoptosis-related cysteine peptidase	0.003516	-1.25129
LPAR4	lysophosphatidic acid receptor 4	0.005372	-1.25127
GNA12	guanine nucleotide binding protein (G protein) alpha 12	0.009051	-1.2511
CYP2W1	cytochrome P450, family 2, subfamily W, polypeptide 1	0.00037	-1.25048
---	---	0.005763	-1.25006
RAX	retina and anterior neural fold homeobox	0.002983	-1.24963
C4A /// C4B /// LOC100292046 /// LOC100294156	complement component 4A (Rodgers blood group) /// complement component 4B (Chido blood	0.002229	-1.24845
ELAVL4	ELAV (embryonic lethal, abnormal vision, Drosophila)-like 4 (Hu antigen D)	0.005864	-1.24796
PXN	paxillin	0.00025	-1.24781
ESR2	estrogen receptor 2 (ER beta)	0.000571	-1.24778

MYL10	myosin, light chain 10, regulatory	0.002715	-1.24748
EFS	embryonal Fyn-associated substrate	0.004955	-1.24747
TFF3	trefoil factor 3 (intestinal)	0.000444	-1.24739
ADAM22	ADAM metallopeptidase domain 22	0.000495	-1.24728
SRPK1	SFRS protein kinase 1	0.008451	-1.24704
LOC441601	septin 7 pseudogene	8.14E-05	-1.24632
BIRC5	baculoviral IAP repeat-containing 5	0.000591	-1.24548
CCT8L2	chaperonin containing TCP1, subunit 8 (theta)-like 2	0.0033	-1.24521
PPAP2B	phosphatidic acid phosphatase type 2B	0.008026	-1.2452
CMA1	chymase 1, mast cell	0.000993	-1.245
APOA2	apolipoprotein A-II	0.000594	-1.24371
KDELR2	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 2	0.007788	-1.24358
ASCL3	achaete-scute complex homolog 3 (Drosophila)	0.00054	-1.24293
RUNX1	runt-related transcription factor 1	0.0054	-1.24289

BUB1	budding uninhibited by benzimidazoles 1 homolog (yeast)	0.000294	-1.24284
---	---	0.003969	-1.24241
SLC6A8	solute carrier family 6 (neurotransmitter transporter, creatine), member 8	0.000656	-1.24067
HNRNPC /// HNRNPCL1 /// LOC440563 /// LOC649330	heterogeneous nuclear ribonucleoprotein C (C1/C2) /// heterogeneous nuclear ribonucleop	0.008367	-1.24043
RIBC2	RIB43A domain with coiled-coils 2	4.24E-05	-1.24036
CLIC4	chloride intracellular channel 4	0.005848	-1.24019
RAB17	RAB17, member RAS oncogene family	0.001346	-1.24001
SCML2	sex comb on midleg-like 2 (Drosophila)	0.008595	-1.23921
SPINLW1	serine peptidase inhibitor-like, with Kunitz and WAP domains 1 (eppin)	9.13E-05	-1.23909
ANK1	ankyrin 1, erythrocytic	0.006497	-1.23867
EDA2R	ectodysplasin A2 receptor	0.004698	-1.2385
---	---	0.003041	-1.23803
---	---	0.000661	-1.23797

HTR4	5-hydroxytryptamine (serotonin) receptor 4	1.84E-05	-1.2378
CDC42EP4	CDC42 effector protein (Rho GTPase binding) 4	0.001214	-1.23768
KANK2	KN motif and ankyrin repeat domains 2	0.000895	-1.23765
ANK1	ankyrin 1, erythrocytic	0.009625	-1.2373
ITGB3	integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)	0.001114	-1.23728
SYN1	synapsin I	0.005147	-1.23728
DUX3 /// DUX4 /// FRG2C /// HPX-2 /// LOC100134409 /// LOC652119 /// LOC653543 /// LOC653544 /// LOC653545 /// LOC728410	double homeobox, 3 /// double homeobox, 4 /// FSHD region gene 2 family, member C /// s	0.007355	-1.23705
PKNOX2	PBX/knotted 1 homeobox 2	0.005082	-1.23701
MLLT4	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocate	0.002526	-1.23601
APOA2	apolipoprotein A-II	0.004185	-1.23591
PENK	proenkephalin	0.000174	-1.23569

GNAT1	guanine nucleotide binding protein (G protein), alpha transducing activity polypeptide	0.00958	-1.23545
FURIN	furin (paired basic amino acid cleaving enzyme)	0.006444	-1.23543
SEMA6A	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6A	0.000683	-1.23507
EGFL6	EGF-like-domain, multiple 6	0.000502	-1.23478
HRH1	histamine receptor H1	0.008279	-1.23466
TSPAN1	tetraspanin 1	0.002802	-1.23452
DBC1	deleted in bladder cancer 1	0.001766	-1.23445
TRPC7	transient receptor potential cation channel, subfamily C, member 7	2.45E-07	-1.23402
MDM2	Mdm2 p53 binding protein homolog (mouse)	0.008092	-1.23388
GPR52	G protein-coupled receptor 52	0.000198	-1.23387
HAMP	hepcidin antimicrobial peptide	0.006054	-1.2333
PRSS2	protease, serine, 2 (trypsin 2)	0.001936	-1.2322

GPR107	G protein-coupled receptor 107	0.008739	-1.23212
FLJ11292	hypothetical protein FLJ11292	5.57E-05	-1.23211
FLJ20184	hypothetical protein FLJ20184	0.005162	-1.23203
B4GALT1	UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 1	0.000192	-1.23117
NKX3-1	NK3 homeobox 1	0.009204	-1.23108
ASIP	agouti signaling protein, nonagouti homolog (mouse)	0.002916	-1.23063
SMAD4	SMAD family member 4	0.004268	-1.2306
EFCAB6	EF-hand calcium binding domain 6	0.000165	-1.23058
GPR20	G protein-coupled receptor 20	0.008518	-1.23016
CA5A	carbonic anhydrase VA, mitochondrial	0.004021	-1.22996
PLK4	polo-like kinase 4 (Drosophila)	0.004056	-1.22981
TAAR5	trace amine associated receptor 5	0.00273	-1.22947
SRPX2	sushi-repeat-containing protein, X-linked 2	0.000298	-1.22939
CNTD2	cyclin N-terminal domain containing 2	1.28E-05	-1.22932
AZGP1	alpha-2-glycoprotein 1, zinc-binding	0.004331	-1.22925

TIMP3	TIMP metallopeptidase inhibitor 3	0.002046	-1.22923
RGS6	regulator of G-protein signaling 6	0.006087	-1.22916
ADARB1	adenosine deaminase, RNA-specific, B1 (RED1 homolog rat)	0.00212	-1.22908
DYNC1I1	dynein, cytoplasmic 1, intermediate chain 1	0.000291	-1.22872
C10orf10	chromosome 10 open reading frame 10	0.001942	-1.22872
PDIA2	protein disulfide isomerase family A, member 2	0.001498	-1.22865
PITX3	paired-like homeodomain 3	0.009246	-1.22861
HOXC13	homeobox C13	8.28E-05	-1.22836
LPAR3	lysophosphatidic acid receptor 3	0.001583	-1.22805
CTRC	chymotrypsin C (caldecrin)	0.008361	-1.22773
CTSL2	cathepsin L2	0.005554	-1.2276
MUC8	mucin 8	0.005519	-1.22759
AQP5	aquaporin 5	0.000994	-1.22755
UGT1A1 /// UGT1A10 /// UGT1A4 /// UGT1A6 /// UGT1A8 /// UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A1 /// UDP glucuronosyltransferase 1	0.001167	-1.22729

KCNQ2	potassium voltage-gated channel, KQT-like subfamily, member 2	0.001293	-1.22727
CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13	0.00551	-1.22653
ZNF155	zinc finger protein 155	0.005718	-1.22653
KIAA0892	KIAA0892	0.000223	-1.22645
ATP2A2	ATPase, Ca++ transporting, cardiac muscle, slow twitch 2	0.008882	-1.22601
MMP26	matrix metallopeptidase 26	0.001265	-1.22581
FGF5	fibroblast growth factor 5	0.003695	-1.22569
FGF18	fibroblast growth factor 18	0.003001	-1.22556
FUT2	fucosyltransferase 2 (secretor status included)	0.003882	-1.22538
SHROOM2	shroom family member 2	0.000419	-1.22534
PRSS3	protease, serine, 3	0.006779	-1.22529
CREB3L1	cAMP responsive element binding protein 3-like 1	0.002111	-1.22516
---	---	0.008631	-1.22511
MGAT2	mannosyl (alpha-1,6-)-glycoprotein beta-1,2-N-acetylglucosaminyltransferase	0.006509	-1.2251
---	---	0.000415	-1.2249

CSF1	colony stimulating factor 1 (macrophage)	0.001088	-1.22487
SMAD3	SMAD family member 3	0.007701	-1.22479
PLCE1	Phospholipase C, epsilon 1	0.005157	-1.22464
MLXIPL	MLX interacting protein-like	0.004864	-1.22443
OR10H3	olfactory receptor, family 10, subfamily H, member 3	0.001893	-1.2243
---	---	0.000353	-1.22418
ABCB11	ATP-binding cassette, sub-family B (MDR/TAP), member 11	0.004152	-1.224
CD84	CD84 molecule	0.009088	-1.22398
ARHGEF4	Rho guanine nucleotide exchange factor (GEF) 4	0.005157	-1.22395
ORC1L	origin recognition complex, subunit 1-like (yeast)	0.003618	-1.22366
PCIF1	PDX1 C-terminal inhibiting factor 1	0.007109	-1.22348
CD177	CD177 molecule	0.000868	-1.22342
---	---	0.000414	-1.22314
C1orf116	chromosome 1 open reading frame 116	0.000626	-1.22307
---	---	0.000385	-1.2228
IFT122	intraflagellar transport 122 homolog (Chlamydomonas)	0.000359	-1.22277
---	---	0.000968	-1.22273

C11orf20	chromosome 11 open reading frame 20	0.002516	-1.2225
DUSP13	dual specificity phosphatase 13	0.000847	-1.22179
C6orf208	chromosome 6 open reading frame 208	0.001257	-1.22163
PLA2G5	phospholipase A2, group V	5.46E-05	-1.22142
PRAMEF1 /// PRAMEF2	PRAME family member 1 /// PRAME family member 2	0.001073	-1.22136
CYP4F8	cytochrome P450, family 4, subfamily F, polypeptide 8	0.001494	-1.22114
KCNA1	potassium voltage-gated channel, shaker-related subfamily, member 1 (episodic ataxia wi	0.00046	-1.22105
MFAP4	microfibrillar-associated protein 4	0.000166	-1.2209
C6	complement component 6	0.006533	-1.22081
SLC4A3	solute carrier family 4, anion exchanger, member 3	0.009715	-1.22068
IL1RAPL1	interleukin 1 receptor accessory protein-like 1	0.000271	-1.22049
SERPINE1	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), me	0.001839	-1.22049

ZCCHC14	zinc finger, CCHC domain containing 14	0.004618	-1.22042
POLR3G	polymerase (RNA) III (DNA directed) polypeptide G (32kD)	0.001007	-1.22028
C16orf68	chromosome 16 open reading frame 68	0.006601	-1.22026
FLJ14100	hypothetical protein FLJ14100	0.003745	-1.22017
SMCHD1	structural maintenance of chromosomes flexible hinge domain containing 1	0.008572	-1.2201
ASCL1	achaete-scute complex homolog 1 (Drosophila)	0.002304	-1.21998
FOXA2	forkhead box A2	0.00025	-1.2197
SLC23A2	solute carrier family 23 (nucleobase transporters), member 2	0.005914	-1.21969
KLK13	kallikrein-related peptidase 13	0.000211	-1.21966
MTSS1L	metastasis suppressor 1-like	0.001589	-1.21956
DNMT3L	DNA (cytosine-5-)-methyltransferase 3-like	0.000936	-1.21952
RREB1	ras responsive element binding protein 1	0.006278	-1.21948
DNMBP	dynamin binding protein	0.007794	-1.21943
PKLR	pyruvate kinase, liver and RBC	0.000571	-1.21918

C1orf106	chromosome 1 open reading frame 106	0.005004	-1.21911
CCDC134	coiled-coil domain containing 134	0.000478	-1.21888
MTSS1	metastasis suppressor 1	0.002441	-1.21878
CCDC40	coiled-coil domain containing 40	0.000701	-1.21869
HOXB1	homeobox B1	0.006406	-1.21825
SCNN1B	sodium channel, nonvoltage-gated 1, beta	0.001488	-1.2182
SEMA4G	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmi	0.002662	-1.2182
RAPGEFL1	Rap guanine nucleotide exchange factor (GEF)-like 1	0.000162	-1.21787
MAGEL2	MAGE-like 2	0.000123	-1.21777
---	---	0.000234	-1.21771
PLSCR2	phospholipid scramblase 2	0.000386	-1.21727
CHD2	chromodomain helicase DNA binding protein 2	0.000841	-1.21722
PLCD1	phospholipase C, delta 1	0.005374	-1.2171
C1orf116	chromosome 1 open reading frame 116	0.006	-1.21704
CHRNA2	cholinergic receptor, nicotinic, alpha 2 (neuronal)	0.008482	-1.21702
MBP	myelin basic protein	0.008574	-1.21675

CDC42BPA	CDC42 binding protein kinase alpha (DMPK-like)	0.000334	-1.21665
TNFRSF11A	tumor necrosis factor receptor superfamily, member 11a, NFKB activator	0.007883	-1.21627
MYF6	myogenic factor 6 (herculin)	0.003356	-1.21615
PI15	peptidase inhibitor 15	0.004832	-1.21612
LOC440895	LIM and senescent cell antigen-like domains 3-like	0.003588	-1.21578
SBF1	SET binding factor 1	0.002572	-1.21568
MAST1	microtubule associated serine/threonine kinase 1	0.001899	-1.21565
GLT8D2	glycosyltransferase 8 domain containing 2	0.000458	-1.21564
ERBB3	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	0.000806	-1.21564
LOH3CR2A	loss of heterozygosity, 3, chromosomal region 2, gene A	0.004412	-1.21562
AMH	anti-Mullerian hormone	0.000237	-1.21552
HR	hairless homolog (mouse)	0.005332	-1.21547
RDH8	retinol dehydrogenase 8 (all-trans)	0.000487	-1.21536
PAWR	PRKC, apoptosis, WT1, regulator	0.005543	-1.2152

DRD3	dopamine receptor D3	0.000203	-1.21493
CCT8	chaperonin containing TCP1, subunit 8 (theta)	0.009015	-1.21463
PRELP	proline/arginine-rich end leucine-rich repeat protein	0.007385	-1.21443
SPOCK3	sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 3	0.000394	-1.21434
EPS8L3	EPS8-like 3	0.007312	-1.21407
NXN	nucleoredoxin	0.003294	-1.21404
SEMA4G	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmi	0.001706	-1.21395
P2RY1	purinergic receptor P2Y, G-protein coupled, 1	0.002207	-1.21385
AVL9	AVL9 homolog (S. cerevisiase)	0.002166	-1.21376
TEK	TEK tyrosine kinase, endothelial	0.000493	-1.21369
MOGAT2	monoacylglycerol O-acyltransferase 2	0.002638	-1.21358
KLK7	kallikrein-related peptidase 7	0.007089	-1.21357
MT1E /// MT1H /// MT1M	metallothionein 1E /// metallothionein 1H /// metallothionein 1M	0.008728	-1.21355
CLDN18	claudin 18	0.002968	-1.21353

RHBDF2	rhomboid 5 homolog 2 (Drosophila)	0.007107	-1.21331
SIX1	SIX homeobox 1	0.006149	-1.21304
INPP5A	inositol polyphosphate-5-phosphatase, 40kDa	0.00971	-1.21301
KCNMB3	potassium large conductance calcium-activated channel, subfamily M beta member 3	0.007976	-1.213
MAP2K5	mitogen-activated protein kinase kinase 5	0.00099	-1.21293
GPD1	glycerol-3-phosphate dehydrogenase 1 (soluble)	0.003338	-1.21278
LPO	lactoperoxidase	0.001326	-1.21277
LOC729143 /// MPRIP	similar to Myosin phosphatase Rho-interacting protein (Rho-interacting protein 3) (M-RI	0.007077	-1.21259
WNT7A	wingless-type MMTV integration site family, member 7A	0.004044	-1.21249
---	---	0.000279	-1.21223
RARG	retinoic acid receptor, gamma	0.002589	-1.21222
CDH7	cadherin 7, type 2	0.004733	-1.2116
MBNL2	muscleblind-like 2 (Drosophila)	0.006252	-1.21154

RASGRP2	RAS guanyl releasing protein 2 (calcium and DAG-regulated)	0.007323	-1.21144
RBMY2FP	RNA binding motif protein, Y-linked, family 2, member F pseudogene	2.59E-05	-1.21141
MASP1	mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive fac	0.009232	-1.2109
CASR	calcium-sensing receptor	0.004273	-1.21088
EGR4	early growth response 4	0.001108	-1.21043
APOC2	apolipoprotein C-II	0.002122	-1.21042
HECW1	HECT, C2 and WW domain containing E3 ubiquitin protein ligase 1	0.005258	-1.2103
HOXB3	homeobox B3	0.003953	-1.21029
IRF5	interferon regulatory factor 5	0.009858	-1.21029
NNMT	nicotinamide N-methyltransferase	0.000406	-1.21028
AOC2	amine oxidase, copper containing 2 (retina-specific)	0.004428	-1.21023
ESRRG	estrogen-related receptor gamma	0.001335	-1.20993
LPIN1	lipin 1	0.009736	-1.20987
ACOT11	acyl-CoA thioesterase 11	0.000945	-1.20973

CCDC33	coiled-coil domain containing 33	0.007172	-1.20945
MBD2	methyl-CpG binding domain protein 2	0.003023	-1.20941
ZNF323	zinc finger protein 323	0.009551	-1.20931
NTRK2	neurotrophic tyrosine kinase, receptor, type 2	0.000251	-1.20921
TMEM151B	transmembrane protein 151B	0.009983	-1.20898
GPLD1	glycosylphosphatidylinositol specific phospholipase D1	0.006394	-1.20848
LENEP	lens epithelial protein	0.000284	-1.20832
HNF1B	HNF1 homeobox B	0.001386	-1.20824
NXPH3	neurexophilin 3	0.001589	-1.20798
---	---	0.006641	-1.20793
ALDH1A3	aldehyde dehydrogenase 1 family, member A3	0.000392	-1.20788
PHF20L1	PHD finger protein 20-like 1	0.002957	-1.20781
CKM	creatine kinase, muscle	0.0008	-1.20774
---	---	0.001361	-1.20746
PARD6B	par-6 partitioning defective 6 homolog beta (C. elegans)	0.000827	-1.20711
CRYGB	crystallin, gamma B	0.005502	-1.20704
HAB1	B1 for mucin	0.001879	-1.20699
LARGE	like-glycosyltransferase	0.009606	-1.20682

RAB40C	RAB40C, member RAS oncogene family	0.00324	-1.20676
MPL	myeloproliferative leukemia virus oncogene	0.007992	-1.20668
CHIT1	chitinase 1 (chitotriosidase)	0.003357	-1.20667
METTL10	methyltransferase like 10	0.003511	-1.20663
DUS4L	dihydrouridine synthase 4-like (S. cerevisiae)	0.00298	-1.20661
PNLIPRP1	pancreatic lipase-related protein 1	0.000459	-1.20659
ELL	elongation factor RNA polymerase II	0.001662	-1.20651
ST8SIA5	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 5	0.000615	-1.20633
ITGA8	integrin, alpha 8	0.009387	-1.20629
GRIN2B	glutamate receptor, ionotropic, N-methyl D-aspartate 2B	0.000406	-1.20603
MC4R	melanocortin 4 receptor	0.00036	-1.20584
RTDR1	rhabdoid tumor deletion region gene 1	0.000275	-1.20581
HDAC6	histone deacetylase 6	0.001545	-1.2058
KCNJ13	potassium inwardly-rectifying channel, subfamily J, member 13	0.001433	-1.20567

CPSF1	cleavage and polyadenylation specific factor 1, 160kDa	1.67E-05	-1.20546
SPANXC	SPANX family, member C	0.001064	-1.2054
CNOT4	CCR4-NOT transcription complex, subunit 4	0.007152	-1.20522
LAMA2	Laminin, alpha 2	7.89E-05	-1.20506
SLC1A6	solute carrier family 1 (high affinity aspartate/glutamate transporter), member 6	0.00372	-1.205
ABCA2	ATP-binding cassette, sub-family A (ABC1), member 2	0.002267	-1.20494
KLK11	kallikrein-related peptidase 11	0.000758	-1.20493
GFRA3	GDNF family receptor alpha 3	0.002967	-1.2047
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4	0.002771	-1.20468
SLC1A3	solute carrier family 1 (glial high affinity glutamate transporter), member 3	0.004552	-1.20467
ATP2B2	ATPase, Ca++ transporting, plasma membrane 2	0.000594	-1.20453
APBB2	amyloid beta (A4) precursor protein-binding, family B, member 2	0.005968	-1.20439

VPS45	vacuolar protein sorting 45 homolog (S. cerevisiae)	0.000839	-1.20431
GHRHR	growth hormone releasing hormone receptor	0.003426	-1.20425
HOXD4	homeobox D4	0.004276	-1.20421
PRPH	peripherin	4.94E-05	-1.20416
ADCY2	adenylate cyclase 2 (brain)	0.006778	-1.20412
LEFTY2	left-right determination factor 2	0.00084	-1.20391
CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1	0.002715	-1.20353
PCP4	Purkinje cell protein 4	2.27E-05	-1.20337
C8B	complement component 8, beta polypeptide	0.0017	-1.2033
RANBP3	RAN binding protein 3	0.001832	-1.2033
PDE6H	phosphodiesterase 6H, cGMP-specific, cone, gamma	0.002496	-1.20303
TRIM15	tripartite motif-containing 15	0.00027	-1.20261
VGLL1	vestigial like 1 (Drosophila)	0.001092	-1.20257
TRIM3	tripartite motif-containing 3	0.000537	-1.20249
LTBP4	latent transforming growth factor beta binding protein 4	0.000462	-1.20238

CRKL	v-crk sarcoma virus CT10 oncogene homolog (avian)-like	0.008611	-1.20236
ADH7	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide	0.000166	-1.20227
PSG3	pregnancy specific beta-1-glycoprotein 3	0.00053	-1.20227
GPR153	G protein-coupled receptor 153	0.008656	-1.20222
MFAP2	microfibrillar-associated protein 2	0.003428	-1.20216
FGF13	fibroblast growth factor 13	0.002263	-1.20212
---	---	0.007125	-1.202
NAPA	N-ethylmaleimide-sensitive factor attachment protein, alpha	0.006488	-1.20191
ALDH3A1	aldehyde dehydrogenase 3 family, memberA1	0.000897	-1.20175
MCM10	minichromosome maintenance complex component 10	0.005216	-1.20168
TLE4	transducin-like enhancer of split 4 (E(sp1) homolog, Drosophila)	0.006143	-1.20166
ITPR3	inositol 1,4,5-triphosphate receptor, type 3	0.006944	-1.20157
CCDC87	coiled-coil domain containing 87	0.001771	-1.20124

C9orf7	chromosome 9 open reading frame 7	0.009273	-1.2011
ACTC1	actin, alpha, cardiac muscle 1	0.00076	-1.20109
OBSL1	obscurin-like 1	0.002861	-1.20096
---	---	0.000232	-1.20095
MAP2	microtubule-associated protein 2	0.003324	-1.20084
CRYM	crystallin, mu	0.005793	-1.20073
RNF122	ring finger protein 122	0.003704	-1.20071
SST	somatostatin	0.003629	-1.2007
HLA-DRB6	major histocompatibility complex, class II, DR beta 6 (pseudogene)	0.009489	-1.20021
SLC22A17	solute carrier family 22, member 17	0.00219	-1.20018
HSPG2	heparan sulfate proteoglycan 2	0.000654	-1.20017
HIP1	huntingtin interacting protein 1	4.28E-05	-1.20004
GRIK2	glutamate receptor, ionotropic, kainate 2	3.13E-06	-1.19991
---	---	0.008492	-1.19976
UNKL	unkempt homolog (Drosophila)-like	0.005034	-1.19954
GPR144	G protein-coupled receptor 144	0.007186	-1.19948
KIR3DX1	killer cell immunoglobulin-like receptor, three domains, X1	0.003825	-1.1993
---	---	0.007994	-1.1993

NARFL	nuclear prelamin A recognition factor-like	0.003052	-1.19926
---	---	0.000127	-1.19903
UCP3	uncoupling protein 3 (mitochondrial, proton carrier)	0.009564	-1.19903
---	---	0.001429	-1.19877
PLXNA2	plexin A2	0.001989	-1.19862
BTN1A1	butyrophilin, subfamily 1, member A1	0.003656	-1.19858
ERCC4	excision repair cross-complementing rodent repair deficiency, complementation group 4	0.007138	-1.19837
CIITA	class II, major histocompatibility complex, transactivator	0.008237	-1.1982
EGFR	epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homo	0.008886	-1.19797
---	---	0.005458	-1.19781
KRT33A	keratin 33A	0.006693	-1.19769
CLTB	Clathrin, light chain (Lcb)	0.008512	-1.19768
B3GALT5	UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 5	0.001241	-1.19754
---	---	0.009616	-1.19751

AP3M2	adaptor-related protein complex 3, mu 2 subunit	0.002731	-1.19749
GJC1	gap junction protein, gamma 1, 45kDa	0.009693	-1.19749
MYO3A	myosin IIIA	0.000406	-1.19726
ADAM12	ADAM metallopeptidase domain 12	0.000608	-1.19713
ARHGAP1	Rho GTPase activating protein 1	0.001148	-1.19713
PPP2R3A	protein phosphatase 2 (formerly 2A), regulatory subunit B", alpha	0.002	-1.19703
CLIC4	chloride intracellular channel 4	0.00595	-1.19699
C20orf195	chromosome 20 open reading frame 195	0.005195	-1.19672
SIGLEC8	sialic acid binding Ig-like lectin 8	0.000256	-1.19653
GPRC5A	G protein-coupled receptor, family C, group 5, member A	0.002762	-1.19624
CACNB1	calcium channel, voltage-dependent, beta 1 subunit	0.003107	-1.19613
MYL10	myosin, light chain 10, regulatory	0.009335	-1.19609
PRLR	prolactin receptor	0.000985	-1.19602
OR2S2	olfactory receptor, family 2, subfamily S, member 2	0.003564	-1.19593

NCR2	Natural cytotoxicity triggering receptor 2	0.005113	-1.19575
CHAF1B	chromatin assembly factor 1, subunit B (p60)	8.04E-05	-1.19574
EYA3	eyes absent homolog 3 (Drosophila)	0.005876	-1.19566
CDS1	CDP-diacylglycerol synthase (phosphatidate cytidylyltransferase) 1	0.006301	-1.19565
FBXL18	F-box and leucine-rich repeat protein 18	6.72E-06	-1.1956
---	---	3.49E-05	-1.19547
---	---	0.006093	-1.19544
ADAM22	ADAM metallopeptidase domain 22	0.000119	-1.19543
ACTL6B	actin-like 6B	0.001385	-1.19543
ZNF821	zinc finger protein 821	0.002862	-1.19538
C16orf71	chromosome 16 open reading frame 71	0.006501	-1.19537
HBBP1	hemoglobin, beta pseudogene 1	0.006504	-1.19525
PLXNA1	plexin A1	0.003653	-1.1951
CDC45L	CDC45 cell division cycle 45-like (S. cerevisiae)	0.00364	-1.19488
MTCP1	mature T-cell proliferation 1	0.002145	-1.19479
PLCB4	phospholipase C, beta 4	0.006205	-1.19469

PLVAP	plasmalemma vesicle associated protein	0.007844	-1.19456
PROX1	prospero homeobox 1	0.003286	-1.19447
CYP3A43	cytochrome P450, family 3, subfamily A, polypeptide 43	0.004232	-1.19391
IGHG1	Immunoglobulin heavy constant gamma 1 (G1m marker)	0.000798	-1.1939
RECQL5	RecQ protein-like 5	0.00231	-1.19387
IDUA	Iduronidase, alpha-L-	0.007734	-1.19383
DLGAP4	discs, large (Drosophila) homolog-associated protein 4	0.009247	-1.19341
PLXNB1	plexin B1	0.007795	-1.19307
HSD17B14	hydroxysteroid (17-beta) dehydrogenase 14	0.002049	-1.19271
FOXP3	forkhead box P3	0.007901	-1.19261
C19orf26	chromosome 19 open reading frame 26	0.00256	-1.19219
EPB41L1	erythrocyte membrane protein band 4.1-like 1	0.000528	-1.19208
RBBP9	retinoblastoma binding protein 9	0.003886	-1.19197
GJB4	gap junction protein, beta 4, 30.3kDa	0.005636	-1.19173
UPK1B	uroplakin 1B	0.001588	-1.19168

CYP19A1	cytochrome P450, family 19, subfamily A, polypeptide 1	0.002082	-1.1916
LOC55908	hepatocellular carcinoma-associated gene TD26	0.002937	-1.1916
CLDN18	claudin 18	0.003193	-1.1916
C2orf72	chromosome 2 open reading frame 72	0.002873	-1.19147
NTRK3	neurotrophic tyrosine kinase, receptor, type 3	3.09E-05	-1.19142
NRXN2	neurexin 2	0.000836	-1.1914
SPDEF	SAM pointed domain containing ets transcription factor	0.000244	-1.19138
IGH@ /// IGHD /// IGHG1 /// IGHM /// LOC100289944 /// VSIG6	immunoglobulin heavy locus /// immunoglobulin heavy constant delta /// immunoglobulin h	0.001803	-1.19135
ACRV1	acrosomal vesicle protein 1	0.003333	-1.19132
PHLDB1	pleckstrin homology-like domain, family B, member 1	0.001717	-1.1913
SORBS1	sorbin and SH3 domain containing 1	0.00522	-1.19127
---	---	6.67E-05	-1.19122
HAPLN2	hyaluronan and proteoglycan link protein 2	0.001502	-1.19118

FABP3	fatty acid binding protein 3, muscle and heart (mammary-derived growth inhibitor)	0.003523	-1.19097
EFS	embryonal Fyn-associated substrate	0.001768	-1.19081
ACVR1B	activin A receptor, type IB	0.00457	-1.19081
CHST3	carbohydrate (chondroitin 6) sulfotransferase 3	0.001252	-1.19075
UGT2A1 /// UGT2A2	UDP glucuronosyltransferase 2 family, polypeptide A1 /// UDP glucuronosyltransferase 2	0.000599	-1.19065
TAF1	TAF1 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 250kDa	0.007846	-1.1905
MT4	metallothionein 4	0.002292	-1.19047
MFAP3	microfibrillar-associated protein 3	0.008836	-1.19025
ETV5	ets variant 5	0.002412	-1.19021
UBQLN3	ubiquilin 3	0.001961	-1.1902
TBX10	T-box 10	0.001032	-1.19013
---	---	0.00191	-1.18979
GJB1	gap junction protein, beta 1, 32kDa	0.008453	-1.18979

ABO	ABO blood group (transferase A, alpha 1-3-N-acetylgalactosaminyltransferase ; transferas	0.007208	-1.18959
SPINK5	serine peptidase inhibitor, Kazal type 5	0.001357	-1.18917
ATAD4	ATPase family, AAA domain containing 4	0.000327	-1.18914
CDH11	cadherin 11, type 2, OB-cadherin (osteoblast)	0.000198	-1.18913
CARD14	caspase recruitment domain family, member 14	0.002462	-1.18906
ALPP /// ALPPL2	alkaline phosphatase, placental (Regan isozyme) /// alkaline phosphatase, placental-lik	0.001709	-1.18902
CBL	Cas-Br-M (murine) ecotropic retroviral transforming sequence	0.009088	-1.18899
LRP4	low density lipoprotein receptor-related protein 4	0.005919	-1.18889
CDKL2	cyclin-dependent kinase-like 2 (CDC2-related kinase)	0.00225	-1.18883
SSX3	synovial sarcoma, X breakpoint 3	0.002688	-1.18867

DSG2	desmoglein 2	0.006638	-1.18848
SLC45A2	solute carrier family 45, member 2	0.001818	-1.18847
LAMA4	laminin, alpha 4	0.00392	-1.18846
WFDC8	WAP four-disulfide core domain 8	0.001163	-1.18843
HTR7	5-hydroxytryptamine (serotonin) receptor 7 (adenylate cyclase-coupled)	0.001731	-1.18841
EFNB3	ephrin-B3	0.005729	-1.18838
TUBB2B	tubulin, beta 2B	0.000497	-1.18837
OR7E19P	olfactory receptor, family 7, subfamily E, member 19 pseudogene	0.001943	-1.18834
PMS2L4	postmeiotic segregation increased 2-like 4 pseudogene	0.006959	-1.1883
ASAP3	ArfGAP with SH3 domain, ankyrin repeat and PH domain 3	0.000269	-1.18819
FRZB	frizzled-related protein	0.001369	-1.1881
PDLIM4	PDZ and LIM domain 4	0.003582	-1.18805
PVT1	Pvt1 oncogene (non-protein coding)	0.001967	-1.18803
TFR2	transferrin receptor 2	0.00593	-1.18802
AHI1	Abelson helper integration site 1	0.008274	-1.18798
---	---	0.001985	-1.18788

TAF4	TAF4 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 135kDa	0.000919	-1.18784
ADAMTSL2	ADAMTS-like 2	0.008834	-1.18783
CLDN4	claudin 4	0.000164	-1.1878
KIR2DL1 /// KIR2DL2 /// KIR2DL3 /// KIR2DL5A /// KIR2DL5B /// KIR2DS1 /// KIR2DS2 /// KIR2DS3 /// KIR2DS4 /// KIR2DS5 /// KIR3DL2 /// KIR3DL3 /// KIR3DP1 /// LOC727787	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 1 /// kil	0.000231	-1.1878
RAPGEF5	Rap guanine nucleotide exchange factor (GEF) 5	0.002052	-1.18774
CRMP1	collapsin response mediator protein 1	0.008402	-1.18763
LDB3	LIM domain binding 3	0.000824	-1.18759
---	---	0.001275	-1.18749
F11	coagulation factor XI	0.004401	-1.18745
USP46	ubiquitin specific peptidase 46	0.009226	-1.18742
PTN	pleiotrophin	0.00012	-1.18707

IBSP	integrin-binding sialoprotein	0.000822	-1.18706
SLC9A3	solute carrier family 9 (sodium/hydrogen exchanger), member 3	0.003578	-1.18695
FLRT3	fibronectin leucine rich transmembrane protein 3	0.002107	-1.18691
TRIM17	tripartite motif-containing 17	0.002821	-1.18688
FGF17	fibroblast growth factor 17	0.005417	-1.18682
CAMK1G	calcium/calmodulin-dependent protein kinase IG	0.003767	-1.18654
GLYR1	glyoxylate reductase 1 homolog (Arabidopsis)	0.001708	-1.18625
CSH1	chorionic somatomammotropin hormone 1 (placental lactogen)	0.000163	-1.18612
NTF3	neurotrophin 3	0.002903	-1.18611
ABHD6	abhydrolase domain containing 6	0.000573	-1.18608
TRIM15	tripartite motif-containing 15	0.002896	-1.18596
OR52A1	olfactory receptor, family 52, subfamily A, member 1	0.002896	-1.18579
FGFR2	fibroblast growth factor receptor 2	0.000178	-1.18567
ORAI2	ORAI calcium release-activated calcium modulator 2	0.007127	-1.18563
---	---	0.002783	-1.18518

---	---	0.002321	-1.18507
C17orf53	chromosome 17 open reading frame 53	0.001902	-1.18505
GLP1R	glucagon-like peptide 1 receptor	0.003491	-1.1849
SLIT1	slit homolog 1 (Drosophila)	0.002042	-1.18475
TP63	tumor protein p63	0.006308	-1.18464
DDR1	discoidin domain receptor tyrosine kinase 1	0.007775	-1.18462
CFTR	cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C,	0.000534	-1.18451
DIO2	deiodinase, iodothyronine, type II	0.003653	-1.18445
LETM1	leucine zipper-EF-hand containing transmembrane protein 1	0.005131	-1.18438
ACSM5	acyl-CoA synthetase medium-chain family member 5	0.000303	-1.18437
---	---	0.001738	-1.18434
ACTA1	actin, alpha 1, skeletal muscle	0.003411	-1.18432
NPR1	natriuretic peptide receptor A/guanylate cyclase A (atrionatriuretic peptide receptor A	0.004745	-1.1842

KCND3	potassium voltage-gated channel, Shal-related subfamily, member 3	0.008592	-1.18418
POPDC3	popeye domain containing 3	0.002195	-1.18411
DNAH3	dynein, axonemal, heavy chain 3	0.008169	-1.18403
SPDEF	SAM pointed domain containing ets transcription factor	0.007526	-1.18397
CLEC4M	C-type lectin domain family 4, member M	0.000696	-1.18389
---	---	0.004001	-1.18375
SLC30A3	solute carrier family 30 (zinc transporter), member 3	0.00669	-1.18367
NAGLU	N-acetylglucosaminidase, alpha-	0.002574	-1.18361
AAK1	AP2 associated kinase 1	0.004007	-1.18358
DHX34	DEAH (Asp-Glu-Ala-His) box polypeptide 34	0.002492	-1.18357
NNAT	neuronatin	0.008336	-1.18355
---	---	0.007629	-1.18337
AKAP9	A kinase (PRKA) anchor protein (yotiao) 9	0.00231	-1.18329
ICMT	isoprenylcysteine carboxyl methyltransferase	0.007841	-1.18329
FAM189A1	family with sequence similarity 189, member A1	0.007897	-1.18319

C10orf81	chromosome 10 open reading frame 81	0.009408	-1.18318
MYOZ1	myozenin 1	0.008907	-1.18309
PKNOX2	PBX/knotted 1 homeobox 2	8.10E-05	-1.18298
MGC31957	hypothetical protein MGC31957	0.001407	-1.18284
PRDM11	PR domain containing 11	0.004128	-1.18266
RET	ret proto-oncogene	0.004396	-1.18265
IGHG1	Immunoglobulin heavy constant gamma 1 (G1m marker)	0.002101	-1.18263
XPNPEP2	X-prolyl aminopeptidase (aminopeptidase P) 2, membrane-bound	0.004951	-1.18263
NTRK2	neurotrophic tyrosine kinase, receptor, type 2	7.26E-05	-1.18262
---	---	0.009809	-1.1826
---	---	0.004011	-1.18253
SLC25A10	solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10	0.000841	-1.18243
NR1I2	nuclear receptor subfamily 1, group I, member 2	0.004273	-1.18219
---	---	0.0068	-1.18217
GRM8	glutamate receptor, metabotropic 8	0.002678	-1.18202

OR3A3	olfactory receptor, family 3, subfamily A, member 3	0.001803	-1.18201
GIPR	gastric inhibitory polypeptide receptor	0.001874	-1.1819
PAH	phenylalanine hydroxylase	0.001658	-1.18186
PACRG	PARK2 co-regulated	0.007415	-1.18175
---	---	0.003881	-1.18173
CLN8	ceroid-lipofuscinosis, neuronal 8 (epilepsy, progressive with mental retardation)	0.001987	-1.18166
ZNF215	zinc finger protein 215	0.000173	-1.18165
TRIO	Triple functional domain (PTPRF interacting)	0.003634	-1.1816
TTLL5	tubulin tyrosine ligase-like family, member 5	0.008239	-1.18155
GRM1	glutamate receptor, metabotropic 1	0.004897	-1.18148
PRKG1	protein kinase, cGMP-dependent, type I	0.002024	-1.18147
HHLA1	HERV-H LTR-associating 1	0.008614	-1.18137
LAMA3	laminin, alpha 3	0.002922	-1.18134
PTN	pleiotrophin	0.002345	-1.18131
SLC37A4	solute carrier family 37 (glucose-6-phosphate transporter), member 4	0.006933	-1.18114

HOXC11	homeobox C11	0.000624	-1.18111
SLCO5A1	solute carrier organic anion transporter family, member 5A1	6.88E-05	-1.18102
CA10	carbonic anhydrase X	0.001818	-1.18102
---	---	0.005863	-1.18094
RRBP1	ribosome binding protein 1 homolog 180kDa (dog)	0.000657	-1.1809
SOD3	superoxide dismutase 3, extracellular	0.00355	-1.18082
NTRK3	neurotrophic tyrosine kinase, receptor, type 3	0.003705	-1.18081
CYR61	cysteine-rich, angiogenic inducer, 61	0.003919	-1.18079
STRA6	stimulated by retinoic acid gene 6 homolog (mouse)	0.005735	-1.18068
SLC6A11	solute carrier family 6 (neurotransmitter transporter, GABA), member 11	0.007789	-1.18065
CNOT4	CCR4-NOT transcription complex, subunit 4	0.004365	-1.18064
ATN1	Atrophin 1	0.004412	-1.18059
ITGB4	integrin, beta 4	0.001879	-1.18054
BCAP29	B-cell receptor-associated protein 29	0.005292	-1.18045
---	---	0.004726	-1.18036
NOVA2	neuro-oncological ventral antigen 2	0.00162	-1.18035

---	---	0.005358	-1.18035
RELN	reelin	0.003425	-1.18034
LAMC2	laminin, gamma 2	0.006538	-1.18034
---	---	0.003782	-1.18031
RAD51	RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae)	0.008493	-1.18024
---	---	0.000913	-1.18016
PRSS7	protease, serine, 7 (enterokinase)	0.005123	-1.18016
DCBLD2	discoidin, CUB and LCCL domain containing 2	0.000493	-1.18007
TACR2	tachykinin receptor 2	0.002078	-1.18003
RAB11B	RAB11B, member RAS oncogene family	0.004596	-1.17994
OR2J2	olfactory receptor, family 2, subfamily J, member 2	0.000236	-1.17993
VSNL1	visinin-like 1	0.001379	-1.17992
IFNA17	interferon, alpha 17	0.003586	-1.17985
DPYSL4	dihydropyrimidinase-like 4	0.00248	-1.17961
---	---	0.009056	-1.17959
MGC2889	hypothetical protein MGC2889	0.001552	-1.17951
RRBP1	Ribosome binding protein 1 homolog 180kDa (dog)	0.007965	-1.17935
POLQ	polymerase (DNA directed), theta	0.002209	-1.17934

OR1A2	olfactory receptor, family 1, subfamily A, member 2	7.49E-06	-1.17927
PURA	Purine-rich element binding protein A	0.00771	-1.17918
AIF1	allograft inflammatory factor 1	0.00406	-1.17917
CBS	cystathionine-beta-synthase	0.008348	-1.17902
NECAB2	N-terminal EF-hand calcium binding protein 2	0.003146	-1.17901
PRKCE	protein kinase C, epsilon	0.003727	-1.17899
NOX1	NADPH oxidase 1	0.003303	-1.17898
IHH	Indian hedgehog homolog (Drosophila)	0.001392	-1.17891
EXO1	exonuclease 1	0.002234	-1.17891
GPRIN2	G protein regulated inducer of neurite outgrowth 2	0.005827	-1.17888
PDX1	pancreatic and duodenal homeobox 1	0.003138	-1.17881
GPR12	G protein-coupled receptor 12	0.007938	-1.17835
---	---	0.004616	-1.17827
FAM188A	family with sequence similarity 188, member A	0.005191	-1.17827

HS3ST3B1	heparan sulfate (glucosamine) 3-O-sulfotransferase 3B1	0.003282	-1.17824
ASCL1	achaete-scute complex homolog 1 (Drosophila)	0.000169	-1.17813
ZNF484	zinc finger protein 484	0.000728	-1.1781
SERPINB3	serpin peptidase inhibitor, clade B (ovalbumin), member 3	5.85E-05	-1.17802
CSH1	chorionic somatomammotropin hormone 1 (placental lactogen)	0.000315	-1.178
BCAN	brevican	0.006433	-1.17796
DDN	dendrin	0.005892	-1.17792
DUOX2	dual oxidase 2	0.002385	-1.17761
MORN1	MORN repeat containing 1	0.004195	-1.17751
SLC39A2	solute carrier family 39 (zinc transporter), member 2	0.006145	-1.17751
CLCN7	chloride channel 7	0.00054	-1.17749
RUNX2	runt-related transcription factor 2	0.000734	-1.17741
TTYH1	tweety homolog 1 (Drosophila)	0.001039	-1.17723
ZNF280B	zinc finger protein 280B	0.008339	-1.17716
PAX3	paired box 3	0.000716	-1.17714
LZTS1	leucine zipper, putative tumor suppressor 1	0.009862	-1.17712

SLC8A2	solute carrier family 8 (sodium/calcium exchanger), member 2	0.003583	-1.17706
HAB1	B1 for mucin	0.00946	-1.17705
KIF1A	kinesin family member 1A	0.002068	-1.17694
ARL4D	ADP-ribosylation factor-like 4D	0.002302	-1.17694
UGT2B15	UDP glucuronosyltransferase 2 family, polypeptide B15	0.007983	-1.17694
NACA2	nascent polypeptide-associated complex alpha subunit 2	0.00631	-1.17693
THRB	thyroid hormone receptor, beta (erythroblastic leukemia viral (v-erb-a) oncogene homolo	0.000259	-1.17685
C6orf15	chromosome 6 open reading frame 15	0.004187	-1.17685
---	---	0.008907	-1.17685
GPR176	G protein-coupled receptor 176	0.00317	-1.17651
WSCD1	WSC domain containing 1	0.005206	-1.17645
PLXNB3	plexin B3	0.002725	-1.17642
CADM3	cell adhesion molecule 3	0.008183	-1.17636
HAP1	huntingtin-associated protein 1	2.19E-05	-1.17629

CYP1A2	cytochrome P450, family 1, subfamily A, polypeptide 2	0.003159	-1.17629
SPAM1	sperm adhesion molecule 1 (PH-20 hyaluronidase, zona pellucida binding)	0.000727	-1.17625
IL22RA1	interleukin 22 receptor, alpha 1	0.001309	-1.17617
CDC2L5	cell division cycle 2-like 5 (cholinesterase-related cell division controller)	0.007821	-1.17609
IRX5	iroquois homeobox 5	0.000291	-1.17596
PPFIA2	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein	0.001152	-1.17588
---	---	0.004585	-1.17587
KDELR3	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	0.000471	-1.17559
CEACAM7	carcinoembryonic antigen-related cell adhesion molecule 7	0.005552	-1.17556
KCMF1	potassium channel modulatory factor 1	0.009164	-1.17553
DUOX1	dual oxidase 1	0.008808	-1.17546
---	---	0.000615	-1.17528

CDC27	cell division cycle 27 homolog (S. cerevisiae)	0.009706	-1.17522
HIST2H2AA3	histone cluster 2, H2aa3	0.002777	-1.17519
CAV3	caveolin 3	0.008482	-1.17519
APOA4	apolipoprotein A-IV	0.006002	-1.17518
---	---	0.001198	-1.17511
NPR3	natriuretic peptide receptor C/guanylate cyclase C (atrionatriuretic peptide receptor C	0.004663	-1.1751
PRG3	proteoglycan 3	3.39E-05	-1.17507
TBC1D22B	TBC1 domain family, member 22B	0.004838	-1.17506
TUSC3	tumor suppressor candidate 3	0.000348	-1.175
RIMS2	regulating synaptic membrane exocytosis 2	0.005824	-1.175
CYP4F12	cytochrome P450, family 4, subfamily F, polypeptide 12	0.007756	-1.1748
TBXA2R	thromboxane A2 receptor	0.000835	-1.17478
HBEGF	Heparin-binding EGF-like growth factor	0.001173	-1.17476
PSG9	pregnancy specific beta-1-glycoprotein 9	0.000597	-1.17461
PYGO1	pygopus homolog 1 (Drosophila)	0.000119	-1.17423

RASGRF1	Ras protein-specific guanine nucleotide-releasing factor 1	0.007711	-1.17412
SCN2A	sodium channel, voltage-gated, type II, alpha subunit	0.005444	-1.17405
KLHL1	kelch-like 1 (Drosophila)	0.003584	-1.17404
DTNB	dystrobrevin, beta	0.005577	-1.17402
GREM1	gremlin 1, cysteine knot superfamily, homolog (Xenopus laevis)	0.008798	-1.17396
SNCG	synuclein, gamma (breast cancer-specific protein 1)	0.005937	-1.17388
C22orf24	chromosome 22 open reading frame 24	0.000444	-1.17382
PALM	paralemmin	0.006745	-1.17378
COBLL1	COBL-like 1	0.003288	-1.17374
DNPEP	aspartyl aminopeptidase	0.008863	-1.17361
MNS1	meiosis-specific nuclear structural 1	0.009321	-1.1735
NFATC4	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 4	0.003566	-1.17336
---	---	0.001222	-1.1733
DLC1	deleted in liver cancer 1	0.009225	-1.17318
---	---	0.002702	-1.17316
HSPC072	hypothetical LOC29075	0.003774	-1.17306

MCAM	melanoma cell adhesion molecule	0.00272	-1.17289
CA12	carbonic anhydrase XII	0.006108	-1.17285
CSHL1	chorionic somatomammotropin hormone-like 1	0.000243	-1.17282
RPAIN	RPA interacting protein	0.000483	-1.17274
COL5A2	collagen, type V, alpha 2	0.004487	-1.1727
UGT1A8 /// UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A8 /// UDP glucuronosyltransferase 1	3.79E-05	-1.17265
IGH@ /// IGHA1 /// IGHG1 /// IGHG2 /// IGHG3 /// IGHM /// LOC100126583 /// LOC100290036 /// LOC100290320 /// LOC100293211 /// LOC652494	immunoglobulin heavy locus /// immunoglobulin heavy constant alpha 1 /// immunoglobulin	0.002422	-1.17249
ITGB1	integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, M	0.001351	-1.17248

TGFB2	transforming growth factor, beta 2	0.003578	-1.17248
ACSM5	acyl-CoA synthetase medium-chain family member 5	0.00119	-1.17244
---	---	0.000204	-1.17236
ALOX12P2	arachidonate 12-lipoxygenase pseudogene 2	0.00767	-1.17234
ERBB4	v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	0.006521	-1.17232
CLDN16	claudin 16	0.008608	-1.17225
CIB2	calcium and integrin binding family member 2	0.006423	-1.17213
GALR3	galanin receptor 3	0.001999	-1.1721
MSMB	microseminoprotein, beta-	0.000282	-1.17208
FABP7	fatty acid binding protein 7, brain	0.009982	-1.17199
ATXN3	ataxin 3	0.009922	-1.17197
KCNJ5	potassium inwardly-rectifying channel, subfamily J, member 5	0.00027	-1.17188
TRDN	triadin	0.005982	-1.1718
CYP3A43	cytochrome P450, family 3, subfamily A, polypeptide 43	0.000729	-1.17176
BAZ2A	bromodomain adjacent to zinc finger domain, 2A	0.000788	-1.17174

ACCN4	amiloride-sensitive cation channel 4, pituitary	0.006157	-1.17166
SILV	silver homolog (mouse)	0.001891	-1.17163
DGCR14	DiGeorge syndrome critical region gene 14	0.008083	-1.17146
SEMA6C	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6C	0.003714	-1.17139
DIO2	deiodinase, iodothyronine, type II	0.001589	-1.17126
PTHLH	parathyroid hormone-like hormone	0.000476	-1.17108
CSF3	colony stimulating factor 3 (granulocyte)	0.003909	-1.17105
---	---	0.002628	-1.17103
LEP	leptin	0.006607	-1.17102
PDZRN3	PDZ domain containing ring finger 3	0.006658	-1.171
RGSL1	regulator of G-protein signaling like 1	0.000118	-1.17097
GJA4	gap junction protein, alpha 4, 37kDa	0.002623	-1.17081
F2	coagulation factor II (thrombin)	0.00539	-1.17065
SLC22A6	solute carrier family 22 (organic anion transporter), member 6	0.002803	-1.17063

RASGRF1	Ras protein-specific guanine nucleotide-releasing factor 1	0.000634	-1.17056
MAPRE2	microtubule-associated protein, RP/EB family, member 2	0.000948	-1.17055
PVRL1	poliovirus receptor-related 1 (herpesvirus entry mediator C)	0.008624	-1.17042
AKAP1	A kinase (PRKA) anchor protein 1	0.002224	-1.17036
---	---	0.001632	-1.17035
POMP	proteasome maturation protein	0.00605	-1.17031
SOX21	SRY (sex determining region Y)-box 21	0.003094	-1.17029
DNAH9	dynein, axonemal, heavy chain 9	0.001951	-1.1701
HOXC5	homeobox C5	0.005033	-1.17002
SERHL2	serine hydrolase-like 2	0.007046	-1.17001
KIAA0485	hypothetical LOC57235	0.005249	-1.16992
ITSN1	intersectin 1 (SH3 domain protein)	0.004533	-1.16989
B4GALT1	UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 1	0.008844	-1.16988
NEK2	NIMA (never in mitosis gene a)-related kinase 2	0.002232	-1.16958

NUPR1	nuclear protein, transcriptional regulator, 1	0.007281	-1.16954
CCDC93	coiled-coil domain containing 93	0.009039	-1.16948
EPO	erythropoietin	0.00697	-1.16943
CRABP2	cellular retinoic acid binding protein 2	0.008297	-1.16942
TYRO3	TYRO3 protein tyrosine kinase	0.002608	-1.16924
GOLGA2	golgi autoantigen, golgin subfamily a, 2	0.00754	-1.16892
SEMA3F	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3F	0.008138	-1.1688
BFSP2	beaded filament structural protein 2, phakinin	0.009323	-1.16867
NCAM1	neural cell adhesion molecule 1	0.001786	-1.16866
FOLH1	folate hydrolase (prostate-specific membrane antigen) 1	0.002392	-1.16854
SSX2	synovial sarcoma, X breakpoint 2	0.001495	-1.16849
TMPRSS4	transmembrane protease, serine 4	0.002865	-1.16833
DCN	decorin	0.007122	-1.16824
LPHN3	latrophilin 3	0.000384	-1.16821
POU4F3	POU class 4 homeobox 3	0.008224	-1.1682

CEACAM5	carcinoembryonic antigen-related cell adhesion molecule 5	0.007102	-1.16817
BCL3	B-cell CLL/lymphoma 3	0.006056	-1.16816
---	---	0.001654	-1.16813
EXTL3	exostoses (multiple)-like 3	0.007597	-1.16811
CCNA1	cyclin A1	0.00771	-1.16794
DDR2	discoidin domain receptor tyrosine kinase 2	0.002146	-1.16784
PAX8	paired box 8	0.001053	-1.16778
SOX5	SRY (sex determining region Y)-box 5	0.003283	-1.16769
POU3F1	POU class 3 homeobox 1	0.002775	-1.16762
PEX16	peroxisomal biogenesis factor 16	0.002334	-1.16754
IL4I1 /// NUP62 /// SIGLEC11	interleukin 4 induced 1 /// nucleoporin 62kDa /// sialic acid binding Ig-like lectin 11	0.005035	-1.16752
ALDOB	aldolase B, fructose-bisphosphate	0.000319	-1.16747
GPC3	glypican 3	0.001612	-1.1674
IGFALS	insulin-like growth factor binding protein, acid labile subunit	0.000261	-1.16732
WDR25	WD repeat domain 25	0.004535	-1.16731
FGF1	fibroblast growth factor 1 (acidic)	0.003604	-1.1673

OSR2	odd-skipped related 2 (Drosophila)	0.005103	-1.1673
ARID1A	AT rich interactive domain 1A (SWI-like)	0.007435	-1.16727
GYPA	glycophorin A (MNS blood group)	0.009414	-1.16715
KLK13	kallikrein-related peptidase 13	0.008814	-1.16712
PARVB	parvin, beta	0.000462	-1.16709
LILRB5	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member	0.006486	-1.16709
RIMS2	regulating synaptic membrane exocytosis 2	0.003506	-1.16705
C19orf21	chromosome 19 open reading frame 21	0.003213	-1.16704
HOXD1	homeobox D1	0.00567	-1.16704
PRSS3	protease, serine, 3	0.007816	-1.167
FLT1	fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability	0.002491	-1.16699
ATP6V1C1	ATPase, H+ transporting, lysosomal 42kDa, V1 subunit C1	0.00431	-1.16699
LOX	lysyl oxidase	0.000711	-1.16681
CRYBB3	crystallin, beta B3	0.001902	-1.16676

CA12	carbonic anhydrase XII	0.006921	-1.16662
PRKG2	protein kinase, cGMP-dependent, type II	0.006891	-1.16659
MASP1	mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive fac	0.003795	-1.16655
LOC728395 /// LOC728403 /// TSPY1	testis specific protein, Y-linked 1-like /// similar to Testis-specific Y-encoded prote	9.49E-05	-1.16641
PDCD1	programmed cell death 1	0.004701	-1.16634
GGTLC1	gamma-glutamyltransferase light chain 1	0.004441	-1.16622
AQP8	aquaporin 8	0.004705	-1.16618
IL1F9	interleukin 1 family, member 9	0.00516	-1.16614
KRT16	keratin 16	0.0054	-1.16604
AICDA	activation-induced cytidine deaminase	0.002152	-1.16602
BRD8	bromodomain containing 8	0.005311	-1.16593
C1orf95	Chromosome 1 open reading frame 95	0.003655	-1.16587
OR3A2	olfactory receptor, family 3, subfamily A, member 2	0.006942	-1.16583
---	---	0.002314	-1.1656

PFKFB2	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2	0.001095	-1.16553
---	---	0.007371	-1.16546
FRZB	frizzled-related protein	0.004073	-1.16541
PAK3	p21 protein (Cdc42/Rac)-activated kinase 3	0.001322	-1.16538
MEIS2	Meis homeobox 2	0.005478	-1.16537
ZSCAN2	zinc finger and SCAN domain containing 2	0.007216	-1.16537
MYH7	myosin, heavy chain 7, cardiac muscle, beta	0.00763	-1.16506
VWA1	von Willebrand factor A domain containing 1	0.005843	-1.165
LSAMP	limbic system-associated membrane protein	0.00683	-1.16484
SRC	v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)	0.000259	-1.16471
UGT1A1 /// UGT1A10 /// UGT1A3 /// UGT1A4 /// UGT1A5 /// UGT1A6 /// UGT1A7 /// UGT1A8 /// UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A1 /// UDP glucuronosyltransferase 1	0.002476	-1.16454

DIO1	deiodinase, iodothyronine, type I	0.002692	-1.16452
---	---	0.009224	-1.16449
TADA3L	transcriptional adaptor 3 (NGG1 homolog, yeast)-like	0.00694	-1.16443
F10	coagulation factor X	0.004459	-1.16432
NFASC	neurofascin homolog (chicken)	0.001454	-1.16431
CALCRL	calcitonin receptor-like	0.001263	-1.16423
NBLA00301	Nbla00301	0.008572	-1.16423
MAB21L1	mab-21-like 1 (C. elegans)	0.006335	-1.16412
FBXO42	F-box protein 42	0.002917	-1.16408
COL10A1	collagen, type X, alpha 1	0.003871	-1.16407
CFB	complement factor B	0.003696	-1.16404
SNX7	sorting nexin 7	0.007996	-1.16401
FOXN1	forkhead box N1	0.007972	-1.16365
SRY	sex determining region Y	0.007481	-1.16363
HLF	hepatic leukemia factor	0.009185	-1.16361
CLCA3P	chloride channel accessory 3 (pseudogene)	0.00306	-1.16343
DAZ1 /// DAZ2 /// DAZ3 /// DAZ4	deleted in azoospermia 1 /// deleted in azoospermia 2 /// deleted in azoospermia 3 ///	0.009345	-1.16343
GPR3	G protein-coupled receptor 3	0.001459	-1.16341

TMPRSS11E	transmembrane protease, serine 11E	0.000617	-1.1634
EMID1	EMI domain containing 1	0.009937	-1.1634
KCNMB2	potassium large conductance calcium-activated channel, subfamily M, beta member 2	0.003215	-1.16335
MUC5AC	mucin 5AC, oligomeric mucus/gel-forming	0.003908	-1.16324
SORT1	sortilin 1	0.004071	-1.16318
HIF3A	hypoxia inducible factor 3, alpha subunit	0.001905	-1.16316
---	---	0.005107	-1.16312
MAPK4	mitogen-activated protein kinase 4	0.005343	-1.16312
TCP11L1	t-complex 11 (mouse)-like 1	0.006965	-1.16308
ZZEF1	zinc finger, ZZ-type with EF-hand domain 1	0.009197	-1.16307
DCAF7	DDB1 and CUL4 associated factor 7	0.00843	-1.16305
DMWD	dystrophia myotonica, WD repeat containing	0.005744	-1.16304
CLCA2	chloride channel accessory 2	0.000363	-1.16297
VAC14	Vac14 homolog (S. cerevisiae)	0.004469	-1.16297
CSPG5	chondroitin sulfate proteoglycan 5 (neuroglycan C)	8.48E-05	-1.16282
---	---	0.005222	-1.16268

STMN2	stathmin-like 2	0.006817	-1.16268
MLLT4	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocate	0.003474	-1.16262
GALNT14	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 14 (Ga	0.008433	-1.16262
FGF12	fibroblast growth factor 12	0.000459	-1.16254
MFAP5	microfibrillar associated protein 5	0.008062	-1.16239
SUMO3	SMT3 suppressor of mif two 3 homolog 3 (S. cerevisiae)	0.006747	-1.16225
HTR3A	5-hydroxytryptamine (serotonin) receptor 3A	0.002037	-1.16224
GDF5	growth differentiation factor 5	0.006583	-1.16222
---	---	0.008115	-1.16217
MMP24	matrix metallopeptidase 24 (membrane-inserted)	0.0086	-1.16211
TSSK1B	testis-specific serine kinase 1B	0.001104	-1.16208
CYP2A7P1	cytochrome P450, family 2, subfamily A, polypeptide 7 pseudogene 1	0.002137	-1.16208

MARK1	MAP/microtubule affinity-regulating kinase 1	0.00508	-1.16207
ATP1B2	ATPase, Na+/K+ transporting, beta 2 polypeptide	0.001769	-1.16204
TBX6	T-box 6	0.005223	-1.162
PAX8	paired box 8	0.001211	-1.16199
IL1R1	interleukin 1 receptor, type I	0.002307	-1.16176
RALYL	RALY RNA binding protein-like	0.004265	-1.16172
OR2B2	olfactory receptor, family 2, subfamily B, member 2	0.00135	-1.16157
TAAR3	trace amine associated receptor 3 (gene/pseudogene)	0.00469	-1.16152
C12orf32 /// IGHG1 /// LOC642131	Chromosome 12 open reading frame 32 /// Immunoglobulin heavy constant gamma 1 (G1m mark	0.006624	-1.1615
DICER1	dicer 1, ribonuclease type III	0.003322	-1.16138
MMP28	matrix metallopeptidase 28	0.00533	-1.16138
GLRA3	glycine receptor, alpha 3	0.00029	-1.16137
PPARD	peroxisome proliferator-activated receptor delta	0.007231	-1.1612
HSPA4L	heat shock 70kDa protein 4-like	0.001573	-1.16116

WNT2	wingless-type MMTV integration site family member 2	0.009189	-1.16115
VIPR2	vasoactive intestinal peptide receptor 2	0.005059	-1.16112
CYP2C9	Cytochrome P450, family 2, subfamily C, polypeptide 9	0.001861	-1.16111
SRPX2	sushi-repeat-containing protein, X-linked 2	0.000138	-1.16109
IGSF1	immunoglobulin superfamily, member 1	0.001192	-1.16104
ALPK3	alpha-kinase 3	0.00608	-1.16101
TFPI	tissue factor pathway inhibitor (lipoprotein-associated coagulation inhibitor)	0.006389	-1.16092
KCNS3	potassium voltage-gated channel, delayed-rectifier, subfamily S, member 3	0.003038	-1.16085
MARCH8	membrane-associated ring finger (C3HC4) 8	0.006576	-1.16083
FRMD4B	FERM domain containing 4B	0.000444	-1.1607
TACR3	tachykinin receptor 3	0.00896	-1.16066
FIGF	c-fos induced growth factor (vascular endothelial growth factor D)	0.005183	-1.16058

PDCD6	Programmed cell death 6	0.006092	-1.16044
TNN	tenascin N	0.006607	-1.16044
SPANXB1 /// SPANXB2 /// SPANXF1	SPANX family, member B1 /// SPANX family, member B2 /// SPANX family, member F1	0.001174	-1.16041
RHBDD3	rhomboid domain containing 3	0.000508	-1.16033
SPP2	secreted phosphoprotein 2, 24kDa	0.005711	-1.16031
PDE10A	phosphodiesterase 10A	0.005387	-1.16026
ZNF224	zinc finger protein 224	0.009425	-1.16025
FGL1	fibrinogen-like 1	0.004849	-1.1602
PGAM2	phosphoglycerate mutase 2 (muscle)	0.003588	-1.16019
CADM4	cell adhesion molecule 4	0.004403	-1.1601
APOBEC2	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 2	0.007177	-1.15988
SLC9A5	solute carrier family 9 (sodium/hydrogen exchanger), member 5	0.003795	-1.15983
SERPINA3	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3	0.001263	-1.15982

GNAT1	guanine nucleotide binding protein (G protein), alpha transducing activity polypeptide	1.43E-05	-1.15969
---	---	0.003568	-1.15968
ARHGEF16	Rho guanine exchange factor (GEF) 16	0.004721	-1.15963
SMARCA2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a	0.00734	-1.15962
DNAH9	dynein, axonemal, heavy chain 9	0.009008	-1.15957
RBM26	RNA binding motif protein 26	0.00116	-1.15955
WNT2B	wingless-type MMTV integration site family, member 2B	0.004131	-1.1595
KCNK2	potassium channel, subfamily K, member 2	0.00217	-1.15945
NPBWR2	neuropeptides B/W receptor 2	0.007611	-1.15945
SP2	Sp2 transcription factor	0.002898	-1.15944
---	---	0.001126	-1.1594
TMPRSS11D	transmembrane protease, serine 11D	0.00681	-1.15937
DENND2A	DENN/MADD domain containing 2A	0.003959	-1.15926

TNIP3	TNFAIP3 interacting protein 3	0.006903	-1.15918
---	---	0.009743	-1.15905
STC1	stanniocalcin 1	0.009242	-1.15902
DOCK6	dedicator of cytokinesis 6	0.007919	-1.15896
ADAM5P	ADAM metallopeptidase domain 5 pseudogene	0.004414	-1.1589
SYDE1	synapse defective 1, Rho GTPase, homolog 1 (C. elegans)	0.002852	-1.15886
TNPO2	transportin 2	0.002767	-1.15883
LRTM1	leucine-rich repeats and transmembrane domains 1	0.002691	-1.15877
USH1C	Usher syndrome 1C (autosomal recessive, severe)	0.006427	-1.15873
PDE12	Phosphodiesterase 12	0.007267	-1.15873
SRCAP	Snf2-related CREBBP activator protein	0.004676	-1.15866
OR10J1	olfactory receptor, family 10, subfamily J, member 1	0.005572	-1.15866
OR2H2	olfactory receptor, family 2, subfamily H, member 2	0.000927	-1.15859
KCNJ8	potassium inwardly-rectifying channel, subfamily J, member 8	0.008335	-1.15855
---	---	0.005451	-1.15854

RP11-257K9.7	hypothetical protein LOC100129128	0.002187	-1.15851
DOCK5	dedicator of cytokinesis 5	0.000433	-1.1585
TPD52L1	tumor protein D52-like 1	0.005443	-1.15839
PAEP	progestagen-associated endometrial protein	0.005702	-1.15836
---	---	0.008347	-1.15836
GGA2	golgi associated, gamma adaptin ear containing, ARF binding protein 2	0.005179	-1.15822
PHLDA3	pleckstrin homology-like domain, family A, member 3	0.008165	-1.15821
HES2	hairy and enhancer of split 2 (Drosophila)	0.00726	-1.15816
MLL	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila)	0.00632	-1.15814
PTN	pleiotrophin	0.001451	-1.15812
ITGB6	integrin, beta 6	0.000984	-1.1581
CHRNA6	cholinergic receptor, nicotinic, alpha 6	0.008293	-1.15806
CIB2	calcium and integrin binding family member 2	0.004346	-1.15803
---	---	0.008761	-1.15788
PTPRF	protein tyrosine phosphatase, receptor type, F	0.009748	-1.15777

TM7SF4	transmembrane 7 superfamily member 4	0.007817	-1.15761
DAZ1 /// DAZ2 /// DAZ3 /// DAZ4	deleted in azoospermia 1 /// deleted in azoospermia 2 /// deleted in azoospermia 3 ///	0.001893	-1.15743
ALX1	ALX homeobox 1	0.000867	-1.15731
OR2F1 /// OR2F2	olfactory receptor, family 2, subfamily F, member 1 /// olfactory receptor, family 2, s	0.009833	-1.15725
---	---	0.003275	-1.15723
PLAT	plasminogen activator, tissue	0.005329	-1.15717
---	---	0.00262	-1.15716
HGC6.3	similar to HGC6.3	0.00088	-1.15709
---	---	0.002596	-1.15707
WNT11	wingless-type MMTV integration site family, member 11	0.003994	-1.15705
PGK2	phosphoglycerate kinase 2	0.001775	-1.15699
SNAI2	snail homolog 2 (Drosophila)	0.001463	-1.15694
---	---	0.001954	-1.15682
IL11	interleukin 11	0.005023	-1.15682
COL4A6	collagen, type IV, alpha 6	0.00986	-1.15677
PRUNE2	prune homolog 2 (Drosophila)	0.003014	-1.15675
---	---	0.004631	-1.15658

ANKS1B	ankyrin repeat and sterile alpha motif domain containing 1B	0.000784	-1.15638
---	---	0.008146	-1.1563
LOC81691	exonuclease NEF-sp	0.008969	-1.15628
FERMT2	fermitin family homolog 2 (Drosophila)	0.006573	-1.15622
TIMP3	TIMP metallopeptidase inhibitor 3	0.005686	-1.15618
CST8	cystatin 8 (cystatin-related epididymal specific)	0.006664	-1.15617
CAPN6	calpain 6	0.006576	-1.15614
IDUA	iduronidase, alpha-L-	0.002113	-1.15597
GPR32	G protein-coupled receptor 32	0.000773	-1.15585
AKR1B10	aldo-keto reductase family 1, member B10 (aldose reductase)	0.007442	-1.15571
GRHL2	grainyhead-like 2 (Drosophila)	5.24E-07	-1.15561
FBXO24	F-box protein 24	0.003095	-1.1555
HSF4	heat shock transcription factor 4	0.007043	-1.15548
IGHG1	Immunoglobulin heavy constant gamma 1 (G1m marker)	0.00779	-1.15512

HCN2	hyperpolarization activated cyclic nucleotide-gated potassium channel 2	0.006206	-1.15509
LRP12	low density lipoprotein-related protein 12	0.007931	-1.15508
ADAM18	ADAM metallopeptidase domain 18	0.006422	-1.15501
ITGA2	integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)	0.005786	-1.15485
ARHGEF15	Rho guanine nucleotide exchange factor (GEF) 15	0.003722	-1.15475
UGT1A1 /// UGT1A10 /// UGT1A7 /// UGT1A8	UDP glucuronosyltransferase 1 family, polypeptide A1 /// UDP glucuronosyltransferase 1	0.004274	-1.1547
GUCA2A	guanylate cyclase activator 2A (guanylin)	0.003837	-1.15459
MDK	midkine (neurite growth-promoting factor 2)	0.003419	-1.15451
ITIH1	inter-alpha (globulin) inhibitor H1	0.003175	-1.15449
EGFR	epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homo	0.004643	-1.15435

UGT1A1 /// UGT1A10 /// UGT1A3 /// UGT1A4 /// UGT1A5 /// UGT1A6 /// UGT1A7 /// UGT1A8 /// UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A1 /// UDP glucuronosyltransferase 1	0.008973	-1.15435
MYOG	myogenin (myogenic factor 4)	0.001644	-1.15431
TMSB15A	thymosin beta 15a	0.001935	-1.15428
TLX1	T-cell leukemia homeobox 1	0.005999	-1.15425
EDNRA	endothelin receptor type A	0.002498	-1.15397
LOC100289791	hypothetical protein LOC100289791	0.00917	-1.1539
MDFI	MyoD family inhibitor	0.008115	-1.15389
ZER1	zer-1 homolog (C. elegans)	0.003119	-1.15387
MYH15	myosin, heavy chain 15	0.00261	-1.15381
CDH20	cadherin 20, type 2	0.004804	-1.15374
GPR63	G protein-coupled receptor 63	0.003041	-1.15367
---	---	0.009921	-1.15354
LOC440345 /// LOC440354 /// LOC595101 /// LOC641298 /// SMG1	hypothetical protein LOC440345 /// PI-3-kinase-related kinase SMG-1 pseudogene /// PI-3	0.002618	-1.15347
HOXC10	homeobox C10	0.000495	-1.15345

KRTAP1-1	keratin associated protein 1-1	8.96E-06	-1.15325
ARSD	arylsulfatase D	0.004513	-1.15315
CPLX3 /// LMAN1L	complexin 3 /// lectin, mannose-binding, 1 like	0.004705	-1.15295
IFNA4	interferon, alpha 4	0.004607	-1.15289
ABCC1	ATP-binding cassette, sub-family C (CFTR/MRP), member 1	0.006325	-1.15283
SEMA3E	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3E	0.004174	-1.15277
MRE11A	MRE11 meiotic recombination 11 homolog A (S. cerevisiae)	0.003835	-1.15276
C1QL1	Complement component 1, q subcomponent-like 1	0.004524	-1.15267
LIPF	lipase, gastric	0.00095	-1.15265
TRIM9	tripartite motif-containing 9	0.008678	-1.15258
BBOX1	butyrobetaine (gamma), 2-oxoglutarate dioxygenase (gamma-butyrobetaine hydroxylase) 1	0.001994	-1.15252
LRRC17	leucine rich repeat containing 17	0.005074	-1.15235

WNT2B	wingless-type MMTV integration site family, member 2B	0.006181	-1.15231
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4	0.007633	-1.15227
SI	sucrase-isomaltase (alpha-glucosidase)	0.001001	-1.1522
ANO3	anoctamin 3	0.00341	-1.15219
OBSL1	obscurin-like 1	0.003099	-1.15215
---	---	0.007073	-1.152
CHRD	chordin	0.004608	-1.15192
MSX2	msh homeobox 2	0.009125	-1.15179
PSG1	pregnancy specific beta-1-glycoprotein 1	0.00029	-1.15178
FAM107A	family with sequence similarity 107, member A	0.001347	-1.15167
LRRC37B2	leucine rich repeat containing 37, member B2	0.001053	-1.15156
ANKLE2	Ankyrin repeat and LEM domain containing 2	0.004674	-1.15155
PAX2	paired box 2	0.004533	-1.15149
UNC5B	Unc-5 homolog B (C. elegans)	0.001994	-1.15124
ADCYAP1R1	adenylate cyclase activating polypeptide 1 (pituitary) receptor type I	0.001818	-1.15119
HFE	hemochromatosis	0.0019	-1.15119
---	---	0.006488	-1.15106

SYT1	synaptotagmin I	0.002216	-1.15088
GJC2	gap junction protein, gamma 2, 47kDa	0.006151	-1.15082
LOC100293871	similar to PRO2325	0.005525	-1.15064
FGF8	fibroblast growth factor 8 (androgen-induced)	0.008777	-1.15061
ACRV1	acrosomal vesicle protein 1	0.005022	-1.15056
NRXN1	neurexin 1	0.004617	-1.15047
GDPD2	glycerophosphodiester phosphodiesterase domain containing 2	0.004533	-1.15039
RGS4	regulator of G-protein signaling 4	0.003963	-1.15033
CELA2A	chymotrypsin-like elastase family, member 2A	7.18E-05	-1.15022
IFNW1	interferon, omega 1	0.001727	-1.15017
MLNR	motilin receptor	0.000122	-1.15014
RNF17	ring finger protein 17	0.003651	-1.15006
LAD1	ladinin 1	0.001937	-1.15
GLRA2	glycine receptor, alpha 2	0.006763	-1.14955
RASL12	RAS-like, family 12	0.000306	-1.14945
MAGOH2	mago-nashi homolog 2, proliferation-associated (Drosophila)	0.003414	-1.14942
C6orf54	chromosome 6 open reading frame 54	0.007125	-1.14931
---	---	0.001197	-1.14922

ZNF214	zinc finger protein 214	0.000481	-1.1492
IKBKG	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma	0.005732	-1.14913
AP4E1	adaptor-related protein complex 4, epsilon 1 subunit	0.004158	-1.14904
ZNRF4	zinc and ring finger 4	0.000445	-1.14875
OSBPL10	oxysterol binding protein-like 10	0.008717	-1.14862
C1orf175 /// TTC4	chromosome 1 open reading frame 175 /// tetratricopeptide repeat domain 4	0.002146	-1.14841
PCDHB3	protocadherin beta 3	0.006249	-1.14837
ADRBK1	adrenergic, beta, receptor kinase 1	0.009822	-1.14828
ITSN1	intersectin 1 (SH3 domain protein)	0.002166	-1.14826
XAGE1A /// XAGE1B /// XAGE1C /// XAGE1D /// XAGE1E	X antigen family, member 1A /// X antigen family, member 1B /// X antigen family, membe	0.00656	-1.1482
CDH22	cadherin-like 22	0.008849	-1.14819
FARP2	FERM, RhoGEF and pleckstrin domain protein 2	0.002273	-1.14813
MYT1	myelin transcription factor 1	0.003875	-1.14809

TNC	Tenascin C	0.004194	-1.14799
MUC5AC	mucin 5AC, oligomeric mucus/gel-forming	0.009053	-1.14791
SLC6A15	solute carrier family 6 (neutral amino acid transporter), member 15	0.008601	-1.1479
PP14571	similar to hCG1777210	0.004733	-1.14789
SMR3A /// SMR3B	submaxillary gland androgen regulated protein 3A /// submaxillary gland androgen regula	0.002495	-1.14788
RXRG	retinoid X receptor, gamma	0.006609	-1.14772
SNX1	sorting nexin 1	0.004678	-1.14771
GLP1R	glucagon-like peptide 1 receptor	0.00094	-1.14751
C6orf155	chromosome 6 open reading frame 155	0.000855	-1.14743
ATP1A2	ATPase, Na+/K+ transporting, alpha 2 (+) polypeptide	0.005511	-1.14737
TFAP4	transcription factor AP-4 (activating enhancer binding protein 4)	0.006392	-1.14734
PNPLA2	Patatin-like phospholipase domain containing 2	0.005616	-1.14727
DIRAS3	DIRAS family, GTP-binding RAS-like 3	0.008453	-1.14717
ANO2	anoctamin 2	0.000478	-1.14709

TACSTD2	tumor-associated calcium signal transducer 2	0.003737	-1.14682
MCM3AP	minichromosome maintenance complex component 3 associated protein	0.000118	-1.14681
IL13RA2	interleukin 13 receptor, alpha 2	0.002253	-1.14678
TRIM10	tripartite motif-containing 10	0.005191	-1.14676
RTEL1	regulator of telomere elongation helicase 1	0.008986	-1.14672
PRRX2	paired related homeobox 2	0.006073	-1.14659
TSHB	thyroid stimulating hormone, beta	0.009948	-1.14656
TIMELESS	timeless homolog (Drosophila)	0.005683	-1.14649
FMO1	flavin containing monooxygenase 1	0.006505	-1.14614
KIF18A	kinesin family member 18A	0.009581	-1.14614
KIAA1199	KIAA1199	0.002884	-1.14612
CALB2	calbindin 2	0.005686	-1.14598
MFAP3L	microfibrillar-associated protein 3-like	0.00354	-1.14575
PTGER3	prostaglandin E receptor 3 (subtype EP3)	0.006984	-1.14569
EPAS1	endothelial PAS domain protein 1	0.005676	-1.14564
---	---	0.000263	-1.14559
SQSTM1	sequestosome 1	0.009341	-1.14558

TSPY1	testis specific protein, Y-linked 1	0.002158	-1.14553
CPM	Carboxypeptidase M	0.001695	-1.14545
DLGAP1	discs, large (Drosophila) homolog-associated protein 1	0.000345	-1.14542
CYP4F11	cytochrome P450, family 4, subfamily F, polypeptide 11	0.0029	-1.14536
TLX3	T-cell leukemia homeobox 3	0.003278	-1.14527
PCDHA10	protocadherin alpha 10	0.006222	-1.14513
TAOK2	TAO kinase 2	0.001305	-1.14511
ERC1	ELKS/RAB6-interacting/CAST family member 1	0.002053	-1.14511
TBX2	T-box 2	0.005151	-1.14502
KALRN	kalirin, RhoGEF kinase	0.008586	-1.14478
DICER1	dicer 1, ribonuclease type III	0.000825	-1.14473
PAPPA	pregnancy-associated plasma protein A, pappalysin 1	0.004805	-1.14473
---	---	0.003479	-1.14468
---	---	0.008082	-1.14467
KIF5A	kinesin family member 5A	0.003962	-1.14458
DNAJC22	DnaJ (Hsp40) homolog, subfamily C, member 22	0.007069	-1.14453
---	---	0.006388	-1.14452

OTUB1	OTU domain, ubiquitin aldehyde binding 1	0.007521	-1.14451
ITGBL1	integrin, beta-like 1 (with EGF-like repeat domains)	0.005427	-1.14445
KIAA1644	KIAA1644	0.009294	-1.14444
SEZ6L2	seizure related 6 homolog (mouse)-like 2	0.005712	-1.14434
PCNXL2	pecanex-like 2 (Drosophila)	0.008015	-1.14434
HMHB1	histocompatibility (minor) HB-1	0.003775	-1.14427
ERG	v-ets erythroblastosis virus E26 oncogene homolog (avian)	0.008735	-1.14427
SNTB2	syntrophin, beta 2 (dystrophin-associated protein A1, 59kDa, basic component 2)	0.004153	-1.14426
GJA5	gap junction protein, alpha 5, 40kDa	0.003562	-1.14404
AGTR2	angiotensin II receptor, type 2	0.007867	-1.14384
GJA3	gap junction protein, alpha 3, 46kDa	0.000595	-1.14377
GCK	glucokinase (hexokinase 4)	0.005137	-1.14365
LRRC61	leucine rich repeat containing 61	0.008969	-1.14358

CNTF /// ZFP91 /// ZFP91-CNTF	ciliary neurotrophic factor /// zinc finger protein 91 homolog (mouse) /// ZFP91-CNTF r	0.000997	-1.14357
PDLIM4	PDZ and LIM domain 4	0.008589	-1.14351
MPPED2	metallophosphoesterase domain containing 2	1.95E-05	-1.1435
IFNA10	interferon, alpha 10	0.003286	-1.14346
ACTN2	actinin, alpha 2	0.005077	-1.14343
VGLL1	vestigial like 1 (Drosophila)	0.00531	-1.14337
GJA9	gap junction protein, alpha 9, 59kDa	0.003777	-1.14331
LDLR	low density lipoprotein receptor	0.003143	-1.1433
ANK2	ankyrin 2, neuronal	0.001761	-1.14329
COL1A1	collagen, type I, alpha 1	0.004543	-1.14329
TIMP3	TIMP metallopeptidase inhibitor 3	0.00282	-1.14323
OTOF	otoferlin	0.006622	-1.14322
AGXT	alanine-glyoxylate aminotransferase	0.005384	-1.14318
GLI2	GLI family zinc finger 2	0.008292	-1.14291
TRMT61A	tRNA methyltransferase 61 homolog A (S. cerevisiae)	0.00203	-1.1428
FOXD2	forkhead box D2	0.003543	-1.14275
TMEM212	transmembrane protein 212	0.003253	-1.14258

DENND2A	DENN/MADD domain containing 2A	0.007115	-1.14257
B3GALT1	UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 1	0.003568	-1.14256
SPAG11A	sperm associated antigen 11A	0.006235	-1.14249
MMP16	matrix metallopeptidase 16 (membrane-inserted)	0.008228	-1.1424
PRDM4	PR domain containing 4	0.0049	-1.14239
TF	transferrin	0.004293	-1.14233
ELF5	E74-like factor 5 (ets domain transcription factor)	0.004394	-1.14201
GSC2	goosecoid homeobox 2	0.000273	-1.14181
EPB41L4B	erythrocyte membrane protein band 4.1 like 4B	0.003468	-1.14166
GYG2	glycogenin 2	0.009413	-1.14164
LYZL6	lysozyme-like 6	0.006035	-1.14149
DCHS2	dachsous 2 (Drosophila)	0.006341	-1.14146
OBP2A /// OBP2B	odorant binding protein 2A /// odorant binding protein 2B	0.00776	-1.14144
ANGPTL3	angiopoietin-like 3	0.007619	-1.1414
MYH11	myosin, heavy chain 11, smooth muscle	0.002648	-1.14138
---	---	0.00271	-1.1412
NES	nestin	0.002731	-1.14119

SLC17A1	solute carrier family 17 (sodium phosphate), member 1	0.004803	-1.14111
RBM15B	RNA binding motif protein 15B	0.004537	-1.14109
CSH1	chorionic somatomammotropin hormone 1 (placental lactogen)	0.009332	-1.14094
HTR5A	5-hydroxytryptamine (serotonin) receptor 5A	0.000162	-1.1409
CYP3A7	cytochrome P450, family 3, subfamily A, polypeptide 7	0.00199	-1.1409
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A	0.004894	-1.14084
KCNV2	potassium channel, subfamily V, member 2	0.005931	-1.14082
TOX3	TOX high mobility group box family member 3	0.001764	-1.14064
CLOCK	clock homolog (mouse)	0.006632	-1.14057
---	---	0.006807	-1.14053
MAGEA6	melanoma antigen family A, 6	0.00046	-1.14048
---	---	0.000518	-1.1404
FAM12A	family with sequence similarity 12, member A	0.001548	-1.14036

COL4A3	collagen, type IV, alpha 3 (Goodpasture antigen)	0.007446	-1.14035
S1PR2	sphingosine-1-phosphate receptor 2	0.008163	-1.14034
NAT8	N-acetyltransferase 8 (GCN5-related, putative)	0.002654	-1.14031
ACE2	angiotensin I converting enzyme (peptidyl-dipeptidase A) 2	0.007666	-1.14031
SLC22A6	solute carrier family 22 (organic anion transporter), member 6	0.00816	-1.14031
SLC13A2	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 2	0.005043	-1.14029
MYH4	myosin, heavy chain 4, skeletal muscle	0.009604	-1.14029
APBB2	amyloid beta (A4) precursor protein-binding, family B, member 2	0.009135	-1.14026
RAP1GAP	RAP1 GTPase activating protein	0.007618	-1.14025
SHOX2	short stature homeobox 2	0.004273	-1.14022
SLCO1A2	solute carrier organic anion transporter family, member 1A2	0.003589	-1.14006

ETV1	ets variant 1	0.00888	-1.14001
MAGEA12	melanoma antigen family A, 12	0.003805	-1.13997
PLA2G6	phospholipase A2, group VI (cytosolic, calcium-independent)	0.006425	-1.13996
ADRA1A	adrenergic, alpha-1A-, receptor	0.007465	-1.13995
---	---	0.008637	-1.13992
SYT5	synaptotagmin V	0.004699	-1.1399
GPR161	G protein-coupled receptor 161	0.004773	-1.13989
SEMA3F	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3F	0.006736	-1.13975
CYP3A43	cytochrome P450, family 3, subfamily A, polypeptide 43	0.003382	-1.13964
HOMER2	homer homolog 2 (Drosophila)	0.003535	-1.13961
KCNJ5	potassium inwardly-rectifying channel, subfamily J, member 5	0.005942	-1.13913
PPL	periplakin	0.00221	-1.13899
COL17A1	collagen, type XVII, alpha 1	0.003115	-1.13894
CSHL1	chorionic somatomammotropin hormone-like 1	0.004285	-1.13887
C9orf116	chromosome 9 open reading frame 116	0.004915	-1.13886

PARK2	Parkinson disease (autosomal recessive, juvenile) 2, parkin	0.00541	-1.13885
UGT2B15	UDP glucuronosyltransferase 2 family, polypeptide B15	0.002586	-1.13876
---	---	0.002677	-1.13855
CDK6	cyclin-dependent kinase 6	0.005041	-1.13851
FAM174B	family with sequence similarity 174, member B	0.00769	-1.13845
---	---	6.02E-05	-1.13837
CELA2A /// CELA2B	chymotrypsin-like elastase family, member 2A /// chymotrypsin-like elastase family, mem	0.008746	-1.13825
SPDEF	SAM pointed domain containing ets transcription factor	0.006039	-1.13824
EPB41	erythrocyte membrane protein band 4.1 (elliptocytosis 1, RH-linked)	0.00381	-1.13816
GAB1	GRB2-associated binding protein 1	0.008578	-1.13811
SMAD6	SMAD family member 6	0.002361	-1.13807
SMR3A	submaxillary gland androgen regulated protein 3A	0.004041	-1.13806

PDE6G	phosphodiesterase 6G, cGMP-specific, rod, gamma	0.009564	-1.13803
COL5A1	collagen, type V, alpha 1	0.003287	-1.13787
ABCA6	ATP-binding cassette, sub-family A (ABC1), member 6	0.008623	-1.13787
DMD	dystrophin	0.000248	-1.13783
CYLC2	cylicin, basic protein of sperm head cytoskeleton 2	0.008464	-1.13771
CIDEA	cell death-inducing DFFA-like effector a	0.007254	-1.13768
RAG2	recombination activating gene 2	0.002984	-1.13757
HIST1H2BN	histone cluster 1, H2bn	0.007319	-1.13751
FMO6P	flavin containing monooxygenase 6 pseudogene	0.007564	-1.13747
---	---	0.009453	-1.13738
MAOA	monoamine oxidase A	0.004806	-1.13729
ANKRD53	ankyrin repeat domain 53	0.00488	-1.13725
HAPLN1	hyaluronan and proteoglycan link protein 1	0.00865	-1.13719
MT1M	metallothionein 1M	0.009364	-1.13718
EHD2	EH-domain containing 2	0.006795	-1.13713
GAD2	glutamate decarboxylase 2 (pancreatic islets and brain, 65kDa)	0.007785	-1.13709
CRISP2	cysteine-rich secretory protein 2	0.009143	-1.13708

CSN2	casein beta	0.006005	-1.13695
---	---	0.006648	-1.13691
SULT1C2	sulfotransferase family, cytosolic, 1C, member 2	0.001313	-1.13685
PCDHGA3	protocadherin gamma subfamily A, 3	0.002114	-1.13681
SSX3	synovial sarcoma, X breakpoint 3	0.001106	-1.13668
FGFR2	fibroblast growth factor receptor 2	0.006105	-1.13666
GPR161	G protein-coupled receptor 161	0.00957	-1.13664
ATN1	atrophin 1	0.009835	-1.13654
CHD5	chromodomain helicase DNA binding protein 5	0.007274	-1.13651
A4GALT	alpha 1,4-galactosyltransferase	0.001062	-1.13647
MYBPH	myosin binding protein H	0.007527	-1.13634
CSHL1	chorionic somatomammotropin hormone-like 1	0.002335	-1.1363
---	---	0.004169	-1.13618
NCAPH2	non-SMC condensin II complex, subunit H2	0.0079	-1.13612
CAPN9	calpain 9	0.003071	-1.13597
CNGB1	cyclic nucleotide gated channel beta 1	0.007125	-1.13588

BCAM	basal cell adhesion molecule (Lutheran blood group)	0.00753	-1.13578
DRD5	dopamine receptor D5	0.00281	-1.13557
NR5A2	nuclear receptor subfamily 5, group A, member 2	0.000913	-1.13547
TEF	thyrotrophic embryonic factor	0.004588	-1.13544
ELAVL2	ELAV (embryonic lethal, abnormal vision, Drosophila)-like 2 (Hu antigen B)	0.002205	-1.13541
DGKB	diacylglycerol kinase, beta 90kDa	0.00918	-1.13537
HTR7P	5-hydroxytryptamine (serotonin) receptor 7 pseudogene	0.00209	-1.13524
RHAG	Rh-associated glycoprotein	0.005396	-1.1352
GH2	growth hormone 2	0.006321	-1.13519
---	---	0.000833	-1.13517
---	---	0.00238	-1.13477
COL4A6	collagen, type IV, alpha 6	0.004113	-1.13473
BMP7	bone morphogenetic protein 7	0.005776	-1.13444
---	---	0.008419	-1.13443
---	---	0.007353	-1.13442
SOSTDC1	sclerostin domain containing 1	0.001856	-1.13439
SOX14	SRY (sex determining region Y)-box 14	0.001541	-1.13438

TAS2R9	taste receptor, type 2, member 9	0.002889	-1.13437
LPHN2	latrophilin 2	0.009349	-1.13418
---	---	0.0099	-1.13418
---	---	0.007172	-1.13409
MAP1A	microtubule-associated protein 1A	0.004384	-1.13404
OSGIN2	Oxidative stress induced growth inhibitor family member 2	0.009721	-1.13398
SLC10A2	solute carrier family 10 (sodium/bile acid cotransporter family), member 2	0.006712	-1.13395
FAM13C	family with sequence similarity 13, member C	0.005974	-1.13385
EMX1	empty spiracles homeobox 1	0.005643	-1.13366
FLJ40330	hypothetical LOC645784	0.005033	-1.13365
CHI3L1	chitinase 3-like 1 (cartilage glycoprotein-39)	0.002657	-1.13357
---	---	0.002091	-1.1335
CDH16	cadherin 16, KSP-cadherin	0.004017	-1.13345
SPRR1A	small proline-rich protein 1A	0.00177	-1.13344
LOX	lysyl oxidase	0.008602	-1.13331
---	---	0.009241	-1.13331
CALCB	calcitonin-related polypeptide beta	0.005526	-1.13322

GABBR2	gamma-aminobutyric acid (GABA) B receptor, 2	0.003986	-1.1332
CPB2	carboxypeptidase B2 (plasma)	0.004188	-1.13308
RASL11B	RAS-like, family 11, member B	0.007069	-1.1329
CCDC81	coiled-coil domain containing 81	0.009508	-1.13288
RUNX1	runt-related transcription factor 1	0.006825	-1.13281
CPA1	carboxypeptidase A1 (pancreatic)	0.002754	-1.13221
CLCNKA /// CLCNKB	chloride channel Ka /// chloride channel Kb	0.001569	-1.13213
FHL5	four and a half LIM domains 5	0.008016	-1.13211
THSD7A	thrombospondin, type I, domain containing 7A	0.001208	-1.1321
TFAP2C	transcription factor AP-2 gamma (activating enhancer binding protein 2 gamma)	0.004298	-1.13184
SPAG11B	sperm associated antigen 11B	0.005305	-1.1317
CAP2	CAP, adenylate cyclase-associated protein, 2 (yeast)	0.002715	-1.13166
PODNL1	podocan-like 1	0.00498	-1.13165

SSX4 /// SSX4B	synovial sarcoma, X breakpoint 4 /// synovial sarcoma, X breakpoint 4B	0.009142	-1.13163
---	---	0.008421	-1.13155
G6PC	glucose-6-phosphatase, catalytic subunit	0.006788	-1.13144
RPE65	retinal pigment epithelium-specific protein 65kDa	0.00168	-1.13112
TMEM222	transmembrane protein 222	0.003611	-1.13108
---	---	0.0082	-1.13098
---	---	0.000935	-1.13097
KDR	kinase insert domain receptor (a type III receptor tyrosine kinase)	0.002995	-1.13074
---	---	0.004838	-1.13055
CHP2	calcineurin B homologous protein 2	0.00539	-1.13026
GPR64	G protein-coupled receptor 64	0.001932	-1.13023
TPM2	tropomyosin 2 (beta)	0.008933	-1.13017
TCEB3B	transcription elongation factor B polypeptide 3B (elongin A2)	0.006753	-1.13005
E2F5	E2F transcription factor 5, p130-binding	0.001129	-1.13001
IL5RA	interleukin 5 receptor, alpha	0.003392	-1.12982

AOC3	amine oxidase, copper containing 3 (vascular adhesion protein 1)	0.000247	-1.12972
ABCF3	ATP-binding cassette, sub-family F (GCN20), member 3	0.004992	-1.12966
CPN2	carboxypeptidase N, polypeptide 2	0.006009	-1.12966
ACE	angiotensin I converting enzyme (peptidyl-dipeptidase A) 1	0.00879	-1.12948
NRP2	neuropilin 2	0.008745	-1.12938
INPP5J	inositol polyphosphate-5-phosphatase J	0.007608	-1.12935
SMAD9	SMAD family member 9	0.006141	-1.1293
FAM155A	family with sequence similarity 155, member A	0.005057	-1.12928
GART	phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phos	0.00165	-1.12917
PIR	pirin (iron-binding nuclear protein)	0.004128	-1.12911
ZNF467	Zinc finger protein 467	0.006009	-1.12907
ITSN2	intersectin 2	0.001473	-1.12903

NR1D1 /// THRA	nuclear receptor subfamily 1, group D, member 1 /// thyroid hormone receptor, alpha (er	0.001964	-1.12896
RP11-35N6.1	plasticity related gene 3	0.005452	-1.12885
LAMB1	laminin, beta 1	0.006026	-1.12864
EPHB3	EPH receptor B3	0.003783	-1.12857
---	---	0.008156	-1.12856
PLA2R1	phospholipase A2 receptor 1, 180kDa	0.005834	-1.12854
RAPGEF4	Rap guanine nucleotide exchange factor (GEF) 4	0.008542	-1.12853
DNAJC8	DnaJ (Hsp40) homolog, subfamily C, member 8	0.007393	-1.12851
ARSJ	arylsulfatase family, member J	0.002634	-1.12845
TRIM49	tripartite motif-containing 49	0.002053	-1.12832
IL9	interleukin 9	0.003046	-1.12812
GC	group-specific component (vitamin D binding protein)	0.001817	-1.12797
IL12B	interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturat	0.006181	-1.12764
CDH2	cadherin 2, type 1, N-cadherin (neuronal)	0.00855	-1.12758
ATXN3L	ataxin 3-like	0.006981	-1.12737

BTF3L1	basic transcription factor 3, like 1 pseudogene	0.008187	-1.12701
CCL19	chemokine (C-C motif) ligand 19	0.006791	-1.12696
BICC1	bicaudal C homolog 1 (Drosophila)	0.007006	-1.12695
FAM186A	family with sequence similarity 186, member A	0.00559	-1.1268
PTPRF	protein tyrosine phosphatase, receptor type, F	0.004195	-1.12674
TRPC4	transient receptor potential cation channel, subfamily C, member 4	0.009479	-1.12666
TCL6	T-cell leukemia/lymphoma 6	0.009932	-1.12663
CYP4A22	cytochrome P450, family 4, subfamily A, polypeptide 22	0.004269	-1.12654
FUT6	fucosyltransferase 6 (alpha (1,3) fucosyltransferase)	0.001302	-1.12636
MUC1	mucin 1, cell surface associated	0.008714	-1.12624
DKFZP434B2016 /// LOC643313	similar to hypothetical protein LOC284701 /// similar to hypothetical protein LOC284701	0.002252	-1.12623
---	---	0.005094	-1.12618

LDHA	lactate dehydrogenase A	0.009545	-1.12609
---	---	0.007472	-1.12582
---	---	0.003741	-1.12572
LOC100131613	PRO1454	0.00409	-1.12556
TRIM3	tripartite motif-containing 3	0.004335	-1.12551
MLLT10	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocate	0.006971	-1.12505
DZIP1	DAZ interacting protein 1	0.003223	-1.12501
ANKRD34C	ankyrin repeat domain 34C	0.000954	-1.12484
BUB1	budding uninhibited by benzimidazoles 1 homolog (yeast)	0.002759	-1.12479
CSPG5	chondroitin sulfate proteoglycan 5 (neuroglycan C)	0.000873	-1.12474
FBLN1	fibulin 1	0.002979	-1.12464
GAD2	glutamate decarboxylase 2 (pancreatic islets and brain, 65kDa)	0.007671	-1.12463
---	---	0.000944	-1.12451
CLDN1	claudin 1	0.002407	-1.12447
CHRNA3	cholinergic receptor, nicotinic, alpha 3	0.006458	-1.12436
SCN11A	sodium channel, voltage-gated, type XI, alpha subunit	0.003796	-1.12417

TEX11	testis expressed 11	0.006239	-1.12409
IL20RA	interleukin 20 receptor, alpha	0.004863	-1.124
AKAP5	A kinase (PRKA) anchor protein 5	0.006577	-1.12361
KBTBD10	kelch repeat and BTB (POZ) domain containing 10	0.005771	-1.12343
MSTN	myostatin	0.001873	-1.1234
TLL2	tolloid-like 2	0.009968	-1.12321
NACAD	NAC alpha domain containing	0.000782	-1.12294
UNC93A	unc-93 homolog A (C. elegans)	0.006006	-1.12294
PTGER1	prostaglandin E receptor 1 (subtype EP1), 42kDa	0.007003	-1.12294
OLAH	oleoyl-ACP hydrolase	0.00896	-1.12289
NHLH2	nescient helix loop helix 2	0.001059	-1.12286
SERPINA6	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 6	0.002411	-1.12272
---	---	0.006655	-1.12253
KRT17	keratin 17	0.003553	-1.12241
---	---	0.006777	-1.12239
KCNMA1	potassium large conductance calcium-activated channel, subfamily M, alpha member 1	0.0067	-1.12228
PRKCA	protein kinase C, alpha	0.006437	-1.12198

STS	steroid sulfatase (microsomal), isozyme S	0.005597	-1.12182
LAMA1	laminin, alpha 1	0.004674	-1.1216
GPR88	G protein-coupled receptor 88	0.008737	-1.1216
ACTN2	actinin, alpha 2	0.003627	-1.12157
TREH	trehalase (brush-border membrane glycoprotein)	0.005379	-1.12152
AKAP4	A kinase (PRKA) anchor protein 4	0.004629	-1.12147
DKK4	dickkopf homolog 4 (Xenopus laevis)	0.005161	-1.1214
---	---	0.007472	-1.12129
PRICKLE3	prickle homolog 3 (Drosophila)	0.007288	-1.12117
IRS4	insulin receptor substrate 4	0.004715	-1.12108
TRPV4	transient receptor potential cation channel, subfamily V, member 4	0.008105	-1.12103
PCDH11Y	protocadherin 11 Y-linked	0.002241	-1.121
---	---	0.009044	-1.12095
APBB2	amyloid beta (A4) precursor protein-binding, family B, member 2	0.002596	-1.12093
SLCO2A1	solute carrier organic anion transporter family, member 2A1	0.004733	-1.12079
---	---	0.00447	-1.12075

DRD2	dopamine receptor D2	0.002588	-1.12059
MTMR7	myotubularin related protein 7	0.009209	-1.12027
ZNF471	zinc finger protein 471	0.004677	-1.12005
TF	transferrin	0.007274	-1.11993
NRIP2	nuclear receptor interacting protein 2	0.005607	-1.11966
ST6GALNAC5	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2	0.005579	-1.11932
COMT	Catechol-O-methyltransferase	0.007202	-1.11926
---	---	0.008063	-1.11915
---	---	0.005963	-1.11891
---	---	0.001254	-1.11889
PAH	phenylalanine hydroxylase	0.002401	-1.11852
LRRC19	leucine rich repeat containing 19	0.003683	-1.11836
PRKAR1B	protein kinase, cAMP-dependent, regulatory, type I, beta	0.007626	-1.11835
HPR	haptoglobin-related protein	0.005044	-1.11829
PRDM5	PR domain containing 5	0.006648	-1.11821
---	---	0.008206	-1.11819
NCRNA00120	non-protein coding RNA 120	0.004933	-1.11814
LOC79999	hypothetical LOC79999	0.008297	-1.11814
ITSN2	intersectin 2	0.004428	-1.118

CACNB2	calcium channel, voltage-dependent, beta 2 subunit	0.008677	-1.11798
GPR98	G protein-coupled receptor 98	0.003265	-1.11788
PREX2	phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 2	0.00758	-1.11779
FAM182B	family with sequence similarity 182, member B	0.008506	-1.11758
LAMA4	laminin, alpha 4	0.001859	-1.11742
---	---	0.008182	-1.117
ARVCF	armadillo repeat gene deletes in velocardiofacial syndrome	0.004203	-1.11699
HAS2	hyaluronan synthase 2	0.005988	-1.11699
YOD1	YOD1 OTU deubiquinating enzyme 1 homolog (S. cerevisiae)	0.007323	-1.11668
---	---	0.003067	-1.11636
PPP2R3A	protein phosphatase 2 (formerly 2A), regulatory subunit B", alpha	0.00874	-1.11635
COL4A1	collagen, type IV, alpha 1	0.002703	-1.11621
---	---	0.005114	-1.11613
RBM12B	RNA binding motif protein 12B	0.004522	-1.11612

TNFRSF11B	tumor necrosis factor receptor superfamily, member 11b	0.009363	-1.11609
GSTA3	glutathione S-transferase alpha 3	0.009885	-1.11598
FAM66D	family with sequence similarity 66, member D	0.007508	-1.11588
OR10H2	olfactory receptor, family 10, subfamily H, member 2	0.001279	-1.11576
PTHLH	parathyroid hormone-like hormone	0.003579	-1.1157
ZNF674	zinc finger family member 674	0.007146	-1.11565
---	---	0.004948	-1.11555
KRT19	keratin 19	0.005928	-1.11545
---	---	0.006606	-1.11543
ACCN2	amiloride-sensitive cation channel 2, neuronal	0.006168	-1.11533
COL6A1	Collagen, type VI, alpha 1	0.006453	-1.11496
---	---	0.007286	-1.11496
LOC100288442 /// LOC100289169 /// LOC728888 /// LOC729602 /// NPIPL2 /// NPIPL3 /// PDXDC2	hypothetical LOC100288442 /// hypothetical protein LOC100289169 /// similar to acyl-CoA	0.008735	-1.11485

SLC37A1	solute carrier family 37 (glycerol-3-phosphate transporter), member 1	0.00935	-1.11481
ATP6V1B1	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B1	0.006862	-1.11475
PTN	pleiotrophin	0.009862	-1.11456
ABI3BP	ABI family, member 3 (NESH) binding protein	0.004323	-1.11452
HR44	Hr44 antigen	0.002042	-1.11417
ZNF324B /// ZNF584	zinc finger protein 324B /// zinc finger protein 584	0.00485	-1.11417
HOXD13	homeobox D13	0.005052	-1.11415
ADH6	alcohol dehydrogenase 6 (class V)	0.00011	-1.11405
IFNA8	interferon, alpha 8	0.004318	-1.1136
---	---	0.001609	-1.1135
---	---	0.002312	-1.11325
MYOZ2	myozenin 2	0.009469	-1.11325
NFATC4	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 4	0.008681	-1.11245
ADAMTS7	ADAM metallopeptidase with thrombospondin type 1 motif, 7	0.007469	-1.11244
FOXL1	forkhead box L1	0.009415	-1.11184

GPR17	G protein-coupled receptor 17	0.009308	-1.11183
SLC18A3	solute carrier family 18 (vesicular acetylcholine), member 3	0.006308	-1.11131
MYH6	myosin, heavy chain 6, cardiac muscle, alpha	0.005188	-1.11125
BOK	BCL2-related ovarian killer	0.008744	-1.111
FGA	fibrinogen alpha chain	0.006323	-1.11088
TEAD4	TEA domain family member 4	0.008474	-1.11075
---	---	0.005611	-1.11074
GRM1	glutamate receptor, metabotropic 1	0.003649	-1.11073
---	---	0.008379	-1.11041
EDNRA	endothelin receptor type A	0.00586	-1.11035
C8orf79	chromosome 8 open reading frame 79	0.008561	-1.11003
METTL7A	methyltransferase like 7A	0.004255	-1.10991
FOLH1	folate hydrolase (prostate-specific membrane antigen) 1	0.002431	-1.10932
RAD54L	RAD54-like (S. cerevisiae)	0.007758	-1.10898
---	---	0.003086	-1.10888
---	---	0.006615	-1.10851
SOX11	SRY (sex determining region Y)-box 11	0.007605	-1.10851
CNOT3	CCR4-NOT transcription complex, subunit 3	0.006753	-1.10843

NTS	neurotensin	0.008975	-1.10791
MAPK12	mitogen-activated protein kinase 12	0.001821	-1.10765
DOCK6	dedicator of cytokinesis 6	0.004973	-1.10674
DNAJC6	DnaJ (Hsp40) homolog, subfamily C, member 6	0.008411	-1.10661
HS3ST3A1	heparan sulfate (glucosamine) 3-O-sulfotransferase 3A1	0.002138	-1.10659
---	---	0.009792	-1.10575
LOC728395 /// TSPY1 /// TSPY3	testis specific protein, Y-linked 1-like /// testis specific protein, Y-linked 1 /// te	0.005872	-1.10572
PTH	parathyroid hormone	0.00392	-1.10538
---	---	0.004436	-1.10502
LAMB4	laminin, beta 4	0.008445	-1.10472
ALDOB	aldolase B, fructose-bisphosphate	0.00586	-1.10469
FLG	filaggrin	0.007077	-1.10448
MLANA	melan-A	0.007622	-1.10421
UBE2D4	ubiquitin-conjugating enzyme E2D 4 (putative)	0.005409	-1.10409
LOC100287483	transcription elongation factor B (SIII), polypeptide 1 pseudogene	0.007954	-1.10403
KRT20	keratin 20	0.00756	-1.10399
---	---	0.009136	-1.10295

POU1F1	POU class 1 homeobox 1	0.009389	-1.10165
SLCO1B3	solute carrier organic anion transporter family, member 1B3	0.003628	-1.10159
CLTA	Clathrin, light chain (Lca)	0.009895	-1.09903
MECOM	MDS1 and EVI1 complex locus	0.009639	-1.09815
C8orf71	chromosome 8 open reading frame 71	0.005004	-1.09779
SULT2A1	sulfotransferase family, cytosolic, 2A, dehydroepiandrosterone (DHEA)-preferring, membe	0.006809	-1.09766
C6orf10	chromosome 6 open reading frame 10	0.007231	-1.09608
---	---	0.00835	-1.09349
SLC27A6	solute carrier family 27 (fatty acid transporter), member 6	0.007873	-1.09267
PRKD1	protein kinase D1	0.00074	-1.09164
SYNPO2L	synaptopodin 2-like	0.003229	-1.0912
THPO	thrombopoietin	0.008285	-1.09086
GABRR1	gamma-aminobutyric acid (GABA) receptor, rho 1	0.008683	-1.09024
CFTR	cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C,	0.003801	-1.0898

PPP2R3A	protein phosphatase 2 (formerly 2A), regulatory subunit B", alpha	0.005056	-1.08882
DCBLD2	discoidin, CUB and LCCL domain containing 2	0.008379	-1.08262
---	---	0.008713	-1.08123
ANP32A /// ANP32C /// ANP32D /// LOC723972	acidic (leucine-rich) nuclear phosphoprotein 32 family, member A /// acidic (leucine-ri	0.007633	-1.07373
XYLT1	xylosyltransferase I	0.002463	1.33229
STAB1	stabilin 1	0.002614	1.46208
STAB1	stabilin 1	0.004388	1.52209
SASH1	SAM and SH3 domain containing 1	0.000209	1.64433
PID1	phosphotyrosine interaction domain containing 1	0.008082	1.65163
FUCA1	fucosidase, alpha-L- 1, tissue	0.00028	1.67342
SASH1	SAM and SH3 domain containing 1	0.000586	2.01341
LRRN3	leucine rich repeat neuronal 3	0.00066	2.52567
LRRN3	leucine rich repeat neuronal 3	0.000927	2.54705

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What is claimed is:

1. A method of predicting clinical responsiveness to laquinimod therapy in a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, the method comprising evaluating expression of a biomarker in the subject, so as to thereby predict clinical responsiveness to laquinimod, wherein the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

2. The method of claim 1, further comprising predicting positive clinical responsiveness to laquinimod if the biomarker is up-regulated in the subject.

3. The method of claim 2, wherein the subject is naïve to laquinimod.

4. The method of claim 1, further comprising predicting positive clinical responsiveness to laquinimod if the biomarker suppressed in the subject.

5. The method of claim 4, wherein the subject has previously received periodic laquinimod administration.

6. The method of claim 5, wherein the subject has received periodic laquinimod administration for at least one month, for at least 6 months, for at least 12 months, or for at least 24 months.

7. The method of any one of claims 1-6, wherein the gene associated with inflammatory response is a gene associated with or involved in TGFb signaling, IL-12 signaling, the pathway of adhesion of phagocytes, chemotaxis of neutrophils, transmigration of leukocytes, caveolar mediated endocytosis, clathrin mediated endocytosis, and/or leukocyte extravasation signaling.

8. The method of any one of claims 1-7, wherein the gene associated with cellular movement is a gene associated with or involved in adhesion and migration of phagocytes, chemotaxis of neutrophils, transmigration of leukocytes, invasion of cells, adhesion of cells, and/or leukocyte extravasation signaling.

9. The method of any one of claims 1-8, wherein the gene associated with cell signaling is a gene associated with or involved in the pathway of adhesion of cells and/or neurotransmission.

10. The method of any one of claims 1-9, wherein the gene associated with cell development is a gene associated with or involved in the pathway of G protein coupled receptor signaling, arachidonic acid metabolism and/or TGFβ signaling.

11. The method of any one of claims 1-10, wherein the gene associated with hematological system is a gene associated with or involved in the pathway of aggregation of blood platelets, activation of blood platelets, aggregation of blood cells, coagulation of blood, intrinsic prothrombin activation pathway and/or coagulation system.

12. The method of any one of claims 1-11, wherein the gene is TNFSF4, SELP, ITFA8, ITGB1/3/5, CXCL5/7, a BMP6 gene, ITGA2/8, ITGβ1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/1R/5/8/13/20/22R, IL-9/11/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, type II BMPR, smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1 or a combination thereof.

13. The method of any one of claims 1-11, wherein the gene is ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-5/20/22, IL-9/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad2/3/4, PAI-1, SELP, ITFA8 , ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-5/13/20/22 , IL-9/11/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1, Alpha tubulin, BMP4/7, MIS, TCF2, IL5R, IL13R, IL20R, ITGB2, NKTR, TEF, CLSTN2, LUC7L2, FABP7, TPTE, FSTL1, SF3B1, LIMS1, PDE5A, XPNPEP1, C5orf4, SPANXB1, SPANXB2, SPANXF1, KRT20, TBC1D1, GRHL2, C5orf4, SEPT6, KIAA1199, SSX2IP, TPM1, CDC14B, USP47, MMRN1, CTNNAL1, SMOX, ALOX12, GLRA3, CA2, GUCY1B3, RFPL1, CLEC1B, GNG11, TSPAN32, RGS10, CALD1, PRKAR2B, CYP4F11, CLCA3P, CELSR3, CDC14B, TPM1, SEPT6, PRKG1, MAX, CCDC93, ARMCX6, LOC653354, TUBB2B, HIST1H2AJ, MFAP3L, LIMS1, GNB5, GPRASP1, SRRT, C1orf116, FBXO7, PPM1A, GUCY1B3,CTDSPL, GNAS, IGF2BP3, TPM1, HIST1H2BK, DLG4, WDR48, CALD1, LOC157627, GNB5, ZNF415,ASAP2, PSD3, GNAS,POPDC3, NRGN, ABLIM3, XYLT1, PTGIS, ARHGEF10, PDGFA,PGRMC1, HIST1H2AC, GNAS, CLDN5, MFAP3L, PGRMC1, MYST3, CAPRIN1, CALD1, FBXW7, DNM3, CD84, PRPF4B, RBM25, WASF3, GRAP2, SPARC, TAL1, NENF, XK, GP1BA,HLA-E, CA5A, LYVE1,MARCH6, NAT8B, TRIM58, RET, SDPR, TBXA2R, TMED10, APBA2, MYL9, POU1F1, H2BFS, HIST1H2BK, FAM12B, VCL, GSPT1, ALDOB, LOC150776, SMPD4, SLC37A1, SPARC, GNAS, TAS2R4, CALM3, POM121, POM121C, GRIK2, GREM1, TNNC2, EPS15L2, ENDOD1, RGS6, SF3B1, TMSB15A, ZBTB20, FUT9, ATP9A,MAX,

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LOC728888, LOC729602, NPIPL2, NPIPL3, PDXDC2, SLC37A1, ATP6V1B1, ABI3BP, HR44, ZNF324B, ZNF584, HOXD13, ADH6, IFNA8, MYOZ2, NFATC4, ADAMTS7, FOXL1, GPR17, SLC18A3, MYH6, BOK, FGA, TEAD4, GRM1, EDNRA, C8orf79, METTL7A, FOLH1, RAD54L, SOX11, CNOT3, NTS, MAPK12, DOCK6, DNAJC6, HS3ST3A1, LOC728395, TSPY1, TSPY3, PTH, LAMB4, ALDOB, FLG, MLANA, UBE2D4, LOC100287483, KRT20, POU1F1, SLCO1B3, CLTA, MECOM, C8orf71, SULT2A1, C6orf10, SLC27A6, PRKD1, SYNPO2L, THPO, GABRR1, CFTR, PPP2R3A, DCBLD2, ANP32A, ANP32C, ANP32D, LOC723972, XYLT1, STAB1, STAB1, SASH1, PID1, FUCA1, SASH1, LRRN3, LRRN3 or a combination thereof.

14. A method of treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome with laquinimod, comprising the steps of:

a) determining whether the subject is a laquinimod responder by evaluating expression of a biomarker in the subject, and

b) administering to the subject an amount of laquinimod effective to treat the subject only if the subject is identified as a laquinimod responder, so as to thereby treat the subject,

wherein the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

15. A method for treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome comprising the steps of:

a) administering to the subject a therapeutically effective amount of laquinimod,

b) determining whether the subject is a laquinimod responder by evaluating expression of a biomarker in the subject; and

c) administering to the subject an amount of laquinimod effective to treat the subject only if the subject is identified as a laquinimod responder, or modifying the administration of laquinimod to the subject if the subject is not identified as a laquinimod responder, so as to thereby treat the subject,

wherein the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

16. The method of claims 14 and 15, wherein the subject is identified as a laquinimod responder if the biomarker is up-regulated in the subject.

17. The method of claims 14 and 15, wherein the subject is identified as a laquinimod responder if the biomarker is suppressed in the subject.

18. The method of any one of claims 14-17, wherein the gene associated with inflammatory response is a gene associated with or involved in TGFb signaling, IL-12 signaling, the pathway of adhesion of phagocytes, chemotaxis of neutrophils, transmigration of leukocytes, caveolar mediated endocytosis, clathrin mediated endocytosis, and/or leukocyte extravasation signaling.

19. The method of any one of claims 14-18, wherein the gene associated with cellular movement is a gene associated with or involved in adhesion and migration of phagocytes, chemotaxis of neutrophils, transmigration of leukocytes, invasion of cells, adhesion of cells, and/or leukocyte extravasation signaling.

20. The method of any one of claims 14-19, wherein the gene associated with cell signaling is a gene associated with or involved in the pathway of adhesion of cells and/or neurotransmission.

21. The method of any one of claims 14-20, wherein the gene associated with cell development is a gene associated with or involved in the pathway of G protein coupled receptor signaling, arachidonic acid metabolism and/or TGFβ signaling.

22. The method of any one of claims 14-21, wherein the gene associated with hematological system is a gene associated with or involved in the pathway of aggregation of blood platelets, activation of blood platelets, aggregation of blood cells, coagulation of blood, intrinsic prothrombin activation pathway and/or coagulation system.

23. The method of any one of claims 14-22, wherein the gene is TNFSF4, SELP, ITFA8, ITGB1/3/5, CXCL5/7, a BMP6 gene, ITGA2/8, ITGβ1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/1R/5/8/13/20/22R, IL-9/11/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, type II BMPR, smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1 or a combination thereof.

24. The method of any one of claims 14-22, wherein the gene is ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-5/20/22, IL-9/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad2/3/4, PAI-1, SELP, ITFA8 , ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28,

ADAM12/18/22, IL-5/13/20/22 , IL-9/11/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1, Alpha tubulin, BMP4/7, MIS, TCF2, IL5R, IL13R, IL20R, ITGB2, NKTR, TEF, CLSTN2, LUC7L2, FABP7, TPTE, FSTL1, SF3B1, LIMS1, PDE5A, XPNPEP1, C5orf4, SPANXB1, SPANXB2, SPANXF1, KRT20, TBC1D1, GRHL2, C5orf4, SEPT6, KIAA1199, SSX2IP, TPM1, CDC14B, USP47, MMRN1, CTNNAL1, SMOX, ALOX12, GLRA3, CA2, GUCY1B3, RFPL1, CLEC1B, GNG11, TSPAN32, RGS10, CALD1, PRKAR2B, CYP4F11, CLCA3P, CELSR3, CDC14B, TPM1, SEPT6, PRKG1, MAX, CCDC93, ARMCX6, LOC653354, TUBB2B, HIST1H2AJ, MFAP3L, LIMS1, GNB5, GPRASP1, SRRT, C1orf116, FBXO7, PPM1A, GUCY1B3,CTDSPL, GNAS, IGF2BP3, TPM1, HIST1H2BK, DLG4, WDR48, CALD1, LOC157627, GNB5, ZNF415,ASAP2, PSD3, GNAS,POPDC3, NRGN, ABLIM3, XYLT1, PTGIS, ARHGEF10, PDGFA,PGRMC1, HIST1H2AC, GNAS, CLDN5, MFAP3L, PGRMC1, MYST3, CAPRIN1, CALD1, FBXW7, DNM3, CD84, PRPF4B, RBM25, WASF3, GRAP2, SPARC, TAL1, NENF, XK, GP1BA,HLA-E, CA5A, LYVE1,MARCH6, NAT8B, TRIM58, RET, SDPR, TBXA2R, TMED10, APBA2, MYL9, POU1F1, H2BFS, HIST1H2BK, FAM12B, VCL, GSPT1, ALDOB, LOC150776, SMPD4, SLC37A1, SPARC, GNAS, TAS2R4, CALM3, POM121, POM121C, GRIK2, GREM1, TNNC2, EPS15L2, ENDOD1, RGS6, SF3B1, TMSB15A, ZBTB20, FUT9, ATP9A,MAX, HIST1H2AI, BAT2D1, ABL1, SNCA, GFI1B, CTSA, SNX13, RPA1, FLNA, XPNPEP1, KIF2A, ZBTB33,PSMD11, UBE2N, FOLR1, TSC22D1, PCNP, CELSR3, ACSBG1, RNF11, SEMA3E, MARCH2, PCDH24, SUPT5H, HLA-E, EGF, HLA-C, FLNA, CDK2AP1, LEPROT, SH3TC2, TUBA4A, MTMR1, TF, PRKD1, NAP1L1, DAB2, FUCA1, HIP1, THPO, MAP1B, PARVB, GP1BB, SEPT5, GJA4, PTGS1, GUCY1A3, HIST1H2AG, GNAS, LRBA, HYAL3, GP6, IGHG1, CYP2A13, CDC14B, MAX, KDM2A, CALD1, GNAZ, C19orf22, ARHGAP6,RHOC, RBX1, GP1BB, SEPT5, PRDX6, PRB4, FLNA, HIST1H2BF, RHBDF2, NUP205, SYT1, EGFL8, PPT2, TUBB1, TMC6, FLJ11292, NAP1L1, ALDH1A3, CSNK1E, PRUNE, COL4A3, ZNF221, ILF3, CABP5, RPA1, ARF1, HIST1H2BI, PTGS1, PRKAA1, GNB5, HIST2H4A, HIST2H4B, CYB5R3, TNS1, DCT, GMPR, ABI3BP, GNAS, SASH1, AAK1, XPO6, CTSL2, QSER1, MAP1LC3B, TBX6, CABP2, MRE11A, MAPRE2, TMC6, BDKRB2, MGLL, HRASLS, WHAMML1, WHAMML2, CLU, STC1, C6orf54, PABPN1, PDLIM1, CLU, PHF20, UBL4A, RNF115, HGD, RASGRP2, PNN, SAPS3, SFI1, GOLGA2, HIST2H2BE, SGEF, HGD, DUS1L, MPP1, HLA-E,GRB14, MMD, ZFHX4, CSNK1G2, HIST1H2BE, MPDZ, B2M, TBXA2R, CTDSPL,SNCA, CD99, POLS, MPL, HIST1H3F, SFRS8, NR5A2, ZMYM2, C6orf10, TMEM40, RNF43, PRUNE, MSH6, PLCB4, PARVB, TOX3,

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25. The method of any one of claims 14-24, wherein laquinimod is administered orally.

26. The method of any one of claims 14-25, wherein laquinimod is administered daily.

27. The method of any one of claims 14-26, wherein laquinimod is administered at a dose of less than 0.6 mg/day, of 0.1-40.0 mg/day, 0.1-2.5 mg/day, 0.25-2.0 mg/day, 0.5-1.2 mg/day, 0.25 mg/day, 0.3 mg/day, 0.5 mg/day, 0.6 mg/day, 1.0 mg/day, 1.2 mg/day, 1.5 mg/day or 2.0 mg/day.

28. The method of any one of claims14-27, wherein the subject is naïve to laquinimod.

29. The method of any one of claims 14-27, wherein the subject has been previously administered laquinimod.

30. The method of any one of claims 14-27, wherein the subject has been previously administered a multiple sclerosis drug other than laquinimod.

31. The method of any one of claims 14-30, wherein the step of evaluating expression of the biomarker comprises normalization of the subject's gene expression.

32. The method of any one of claims 14-31, wherein the step of evaluating expression of the biomarker comprises comparing expression level in the subject relative to a reference value.

33. The method of claim 32, wherein the reference value is based on the level of expression of the biomarker in a laquinimod Non-Responder population.

34. The method of claim 32, wherein the reference value is based on the level of expression of the biomarker in a healthy control population.

35. The method of any one of claims 32-34, wherein the subject is identified as a laquinimod responder if expression of the biomarker is higher than a reference value.

36. The method of any one of claims 32-34, wherein the subject is identified as a laquinimod responder if expression level of the biomarker is lower than a reference value.

37. The method of any one of claims 1-36, wherein expression of the biomarker is evaluated in the blood of the subject.

38. The method of claim 37, wherein expression of the biomarker is evaluated in the peripheral blood mononuclear cells (PBMCs) of the subject.

39. The method of any one of claims 14-38, wherein expression of the biomarker is evaluated prior to treatment with laquinimod.

40. The method of any one of claims 14-38, wherein expression of the biomarker is evaluated after beginning treatment with laquinimod.

41. The method of claim 40, wherein expression of the biomarker is evaluated one month, 6 months, 12 months or 24 months after beginning treatment with laquinimod.

42. The method of any one of claims 14-41, wherein if the subject is identified as a laquinimod responder, the subject is thereafter administered a pharmaceutical composition comprising laquinimod and a pharmaceutically acceptable carrier as monotherapy.

43. The method of any one of claims 14-41, wherein if the subject is identified as a laquinimod responder, the subject is thereafter administered a pharmaceutical composition comprising laquinimod and a pharmaceutically acceptable carrier in combination with another multiple sclerosis drug.

44. The method of any one of claims 14-43, wherein if the subject is identified as a laquinimod non-responder, the subject is thereafter administered a multiple sclerosis drug which is not laquinimod.

45. The method of any one of claims 1-44, wherein the subject is a human patient.

46. Laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein the subject has been identified as a laquinimod responder.

47. A pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein the subject has been identified as a laquinimod responder.

48. Laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is up-regulated and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

49. A pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is up-regulated and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

50. Laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is suppressed and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

51. A pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is suppressed and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

52. A therapeutic package for dispensing to, or for use in dispensing to, a subject identified as a laquinimod responder afflicted with multiple sclerosis or presenting a clinically isolated syndrome, which comprises:

a) one or more unit doses, each such unit dose comprising an amount of laquinimod, and

b) a finished pharmaceutical container therefor, said container containing said unit dose or unit doses, said container further containing or comprising labeling directing the use of said package in the treatment of said subject.

53. A therapeutic package for dispensing to, or for use in dispensing to, a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, which comprises:

a) one or more unit doses, each such unit dose comprising an amount of laquinimod, and

b) a finished pharmaceutical container therefor, said container containing said unit dose or unit doses, said container further containing or comprising labeling directing the use of said package in the treatment of said subject,

wherein expression of a biomarker in the subject is suppressed or up-regulated and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

AMENDED CLAIMS
received by the International Bureau on 05 Feb 2015(05.02.2015)

1. A method of characterizing the response to laquinimod therapy in a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, the method comprising evaluating expression of a biomarker in the subject at baseline, and at least one month after laquinimod administration, so as to thereby characterize the response to laquinimod, wherein the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

2. The method of claim 1, wherein the biomarker is up-regulated in the subject compared to baseline.

3. The method of claim 2, wherein the subject is naïve to laquinimod.

4. The method of claim 1, wherein the biomarker suppressed in the subject compared to baseline.

5. The method of claim 4, wherein the subject has previously received periodic laquinimod administration.

6. The method of claim 5, wherein evaluating expression of a biomarker in the subject is conducted at least one month, at least 6 months, at least 12 months, or at least 24 months after baseline.

7. The method of any one of claims 1-6, wherein the gene associated with inflammatory response is a gene associated with or involved in TGFb signaling, IL-12 signaling, the pathway of adhesion of phagocytes, chemotaxis of neutrophils, transmigration of leukocytes, caveolar mediated endocytosis, clathrin mediated endocytosis, and/or leukocyte extravasation signaling.

8. The method of any one of claims 1-7, wherein the gene associated with cellular movement is a gene associated with or involved in adhesion and migration of phagocytes, chemotaxis of neutrophils, transmigration of leukocytes, invasion of cells, adhesion of cells, and/or leukocyte extravasation signaling.

9. The method of any one of claims 1-8, wherein the gene associated with cell signaling is a gene associated with or involved in the pathway of adhesion of cells and/or neurotransmission.

10. The method of any one of claims 1-9, wherein the gene associated with cell development is a gene associated with or involved in the pathway of G protein coupled receptor signaling, arachidonic acid metabolism and/or TGFβ signaling.

11. The method of any one of claims 1-10, wherein the gene associated with hematological system is a gene associated with or involved in the pathway of aggregation of blood platelets, activation of blood platelets, aggregation of blood cells, coagulation of blood, intrinsic prothrombin activation pathway and/or coagulation system.

12. The method of any one of claims 1-11, wherein the gene is TNFSF4, SELP, ITFA8, ITGB1/3/5, CXCL5/7, a BMP6 gene, ITGA2/8, ITGβ1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-1/1R/5/8/13/20/22R, IL-9/11/12/36, TNFRSF11A/B, IFNA4/8/10/17, TGβ, LTBP4, MEK1/2, TGFβ type 1 receptor, type II BMPR, smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1 or a combination thereof.

13. The method of any one of claims 1-11, wherein the gene is ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-5/20/22, IL-9/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad2/3/4, PAI-1, SELP, ITFA8 , ITGB1/3/5, CXCL5/7, BMP6, ITGA2/8, ITGB1/3/4/5/6, ITGBL1, MMP16/24/26/28, ADAM12/18/22, IL-5/13/20/22 , IL-9/11/36, TNFRSF11A/B, TGβ, LTBP4, MEK1/2, Smad1/2/3/4/5/6/8, PAI-1, CCL19, IKKg, LTBP1, Alpha tubulin, BMP4/7, MIS, TCF2, IL5R, IL13R, IL20R, ITGB2, NKTR, TEF, CLSTN2, LUC7L2, FABP7, TPTE, FSTL1, SF3B1, LIMS1, PDE5A, XPNPEP1, C5orf4, SPANXB1, SPANXB2, SPANXF1, KRT20, TBC1D1, GRHL2, C5orf4, SEPT6, KIAA1199, SSX2IP, TPM1, CDC14B, USP47, MMRN1, CTNNAL1, SMOX, ALOX12, GLRA3, CA2, GUCY1B3, RFPL1, CLEC1B, GNG11, TSPAN32, RGS10, CALD1, PRKAR2B, CYP4F11, CLCA3P, CELSR3, CDC14B, TPM1, SEPT6, PRKG1, MAX, CCDC93, ARMCX6, LOC653354, TUBB2B, HIST1H2AJ, MFAP3L, LIMS1, GNB5, GPRASP1, SRRT, C1orf116, FBXO7, PPM1A, GUCY1B3,CTDSPL, GNAS, IGF2BP3, TPM1, HIST1H2BK, DLG4, WDR48, CALD1, LOC157627, GNB5, ZNF415,ASAP2, PSD3, GNAS,POPDC3, NRGN, ABLIM3, XYLT1, PTGIS, ARHGEF10, PDGFA,PGRMC1, HIST1H2AC, GNAS, CLDN5, MFAP3L, PGRMC1, MYST3, CAPRIN1, CALD1,

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14. The method of any one of claims 1-13, wherein expression of the biomarker is evaluated in the blood of the subject.

15. The method of claim 14, wherein expression of the biomarker is evaluated in the peripheral blood mononuclear cells (PBMCs) of the subject.

16. The method of any one of claims 1-15, wherein the subject is a human patient.

17. Laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein the subject has been identified as a laquinimod responder.

18. A pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein the subject has been identified as a laquinimod responder.

19. Laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is up-regulated and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

20. A pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is up-regulated and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

21. Laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is suppressed and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

22. A pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein expression of a biomarker in the subject is suppressed and the biomarker is a gene associated with inflammatory response, a gene associated with cellular movement, a gene associated with cell signaling, a gene associated with cell development, a gene associated with hematological system, or a combination thereof.

Figure 1B

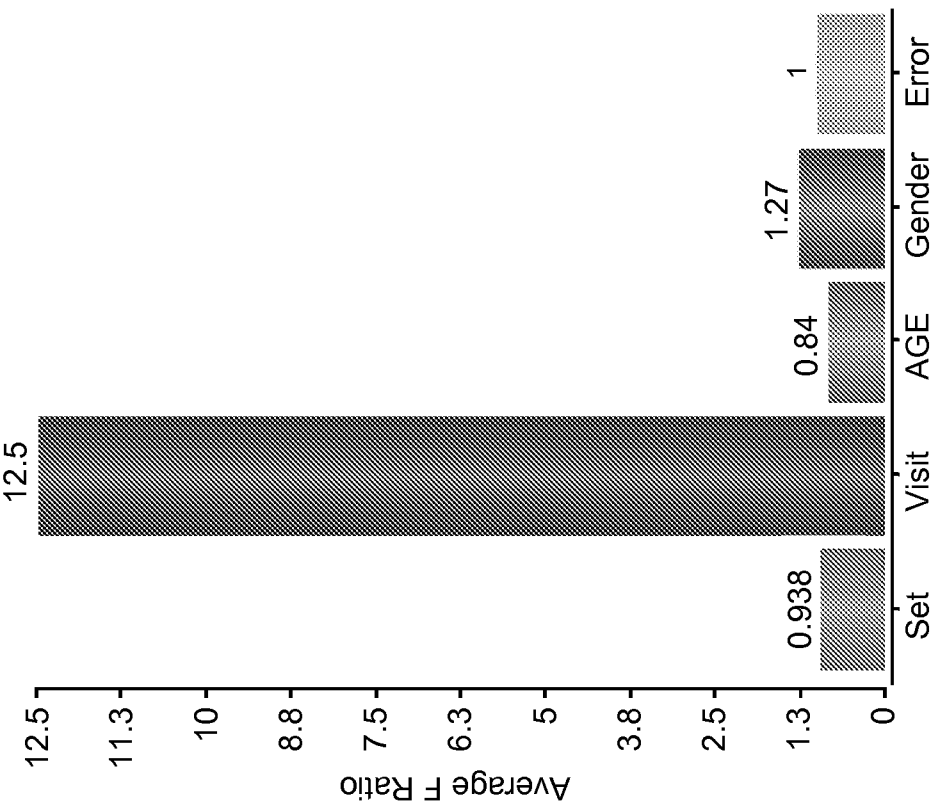


Figure 1A

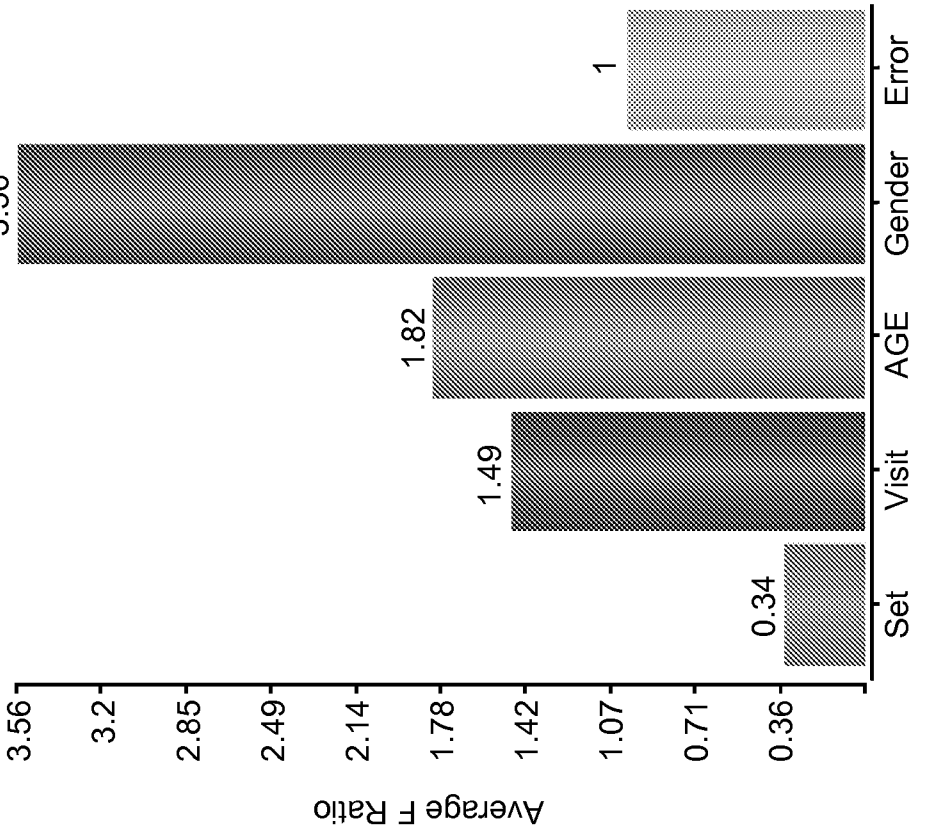


FIGURE 1

Figure 2B

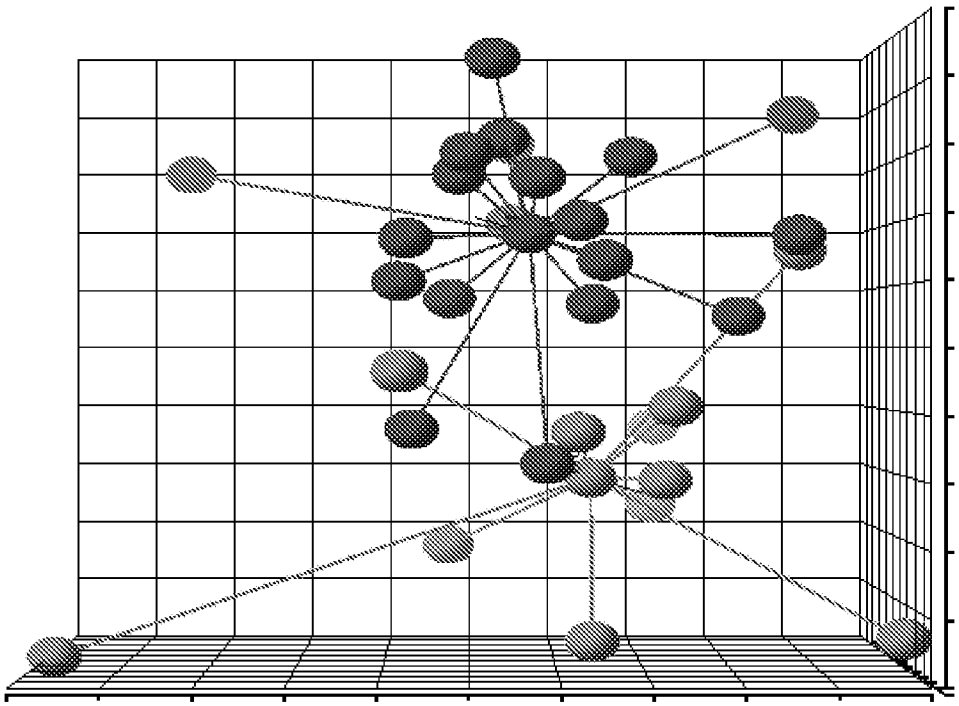


Figure 2A

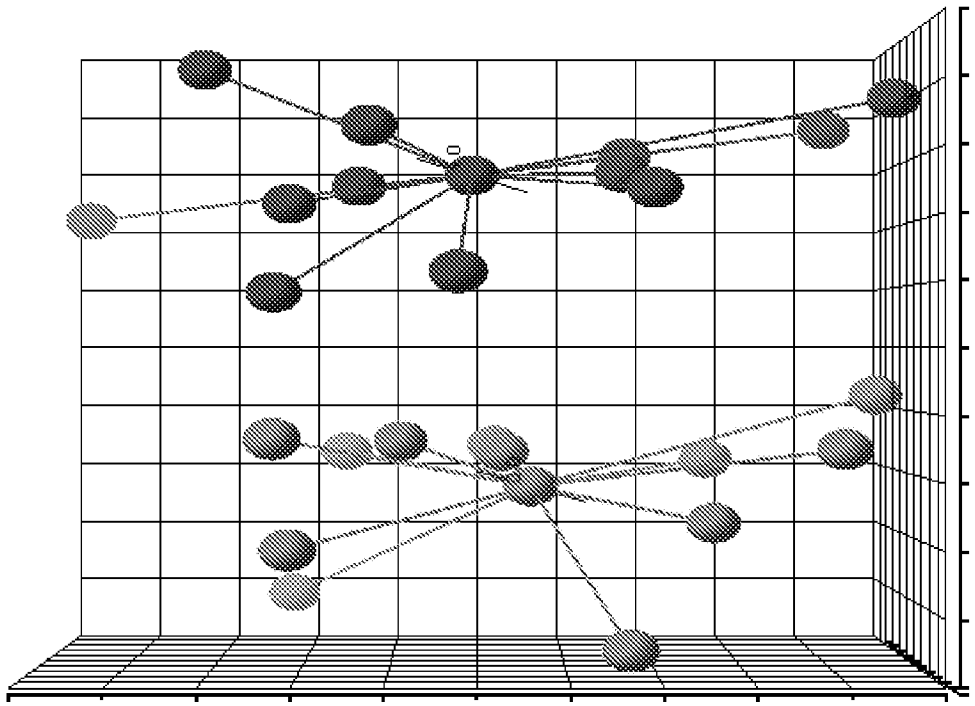


FIGURE 2

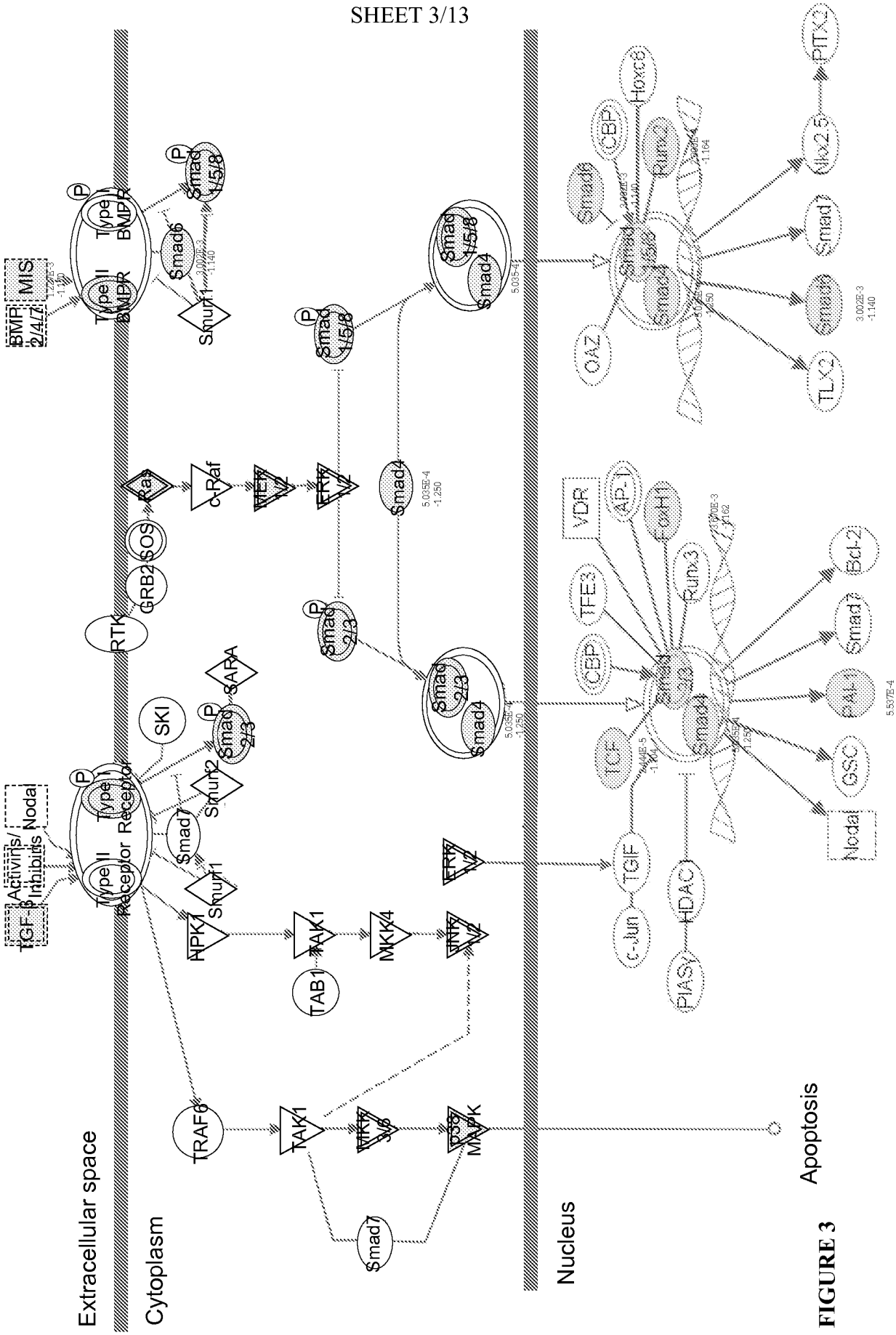

Extracellular space
Cytoplasm
Nucleus
Apoptosis
TGF-β
Activins/
Inhibins
Nodal
BMP
2/4/7
MIS
Type II
Receptor
Type I
BMPR
P
Smad
1/5/8
Smad6
Smurf1
RTK
GRB2
SOS
Ras
c-Raf
MEK
ERK
Smad4
Smad
2/3
SKI
SARA
Smad7
Smurf2
Smurf1
MPK1
TAK1
TAB1
MKK4
JNK
TRAF6
p38
MAPK
TCF
TGIF
c-Jun
HDAC
PIASy
VDR
TFE3
CBP
AP-1
c-JUN
Runx3
Runx2
Smad6
OAZ
Hoxc6
TLX2
Nkx2.5
PITX2
Bcl-2
PAI-1
GSC
Nodal

FIGURE 3

FIGURE 4

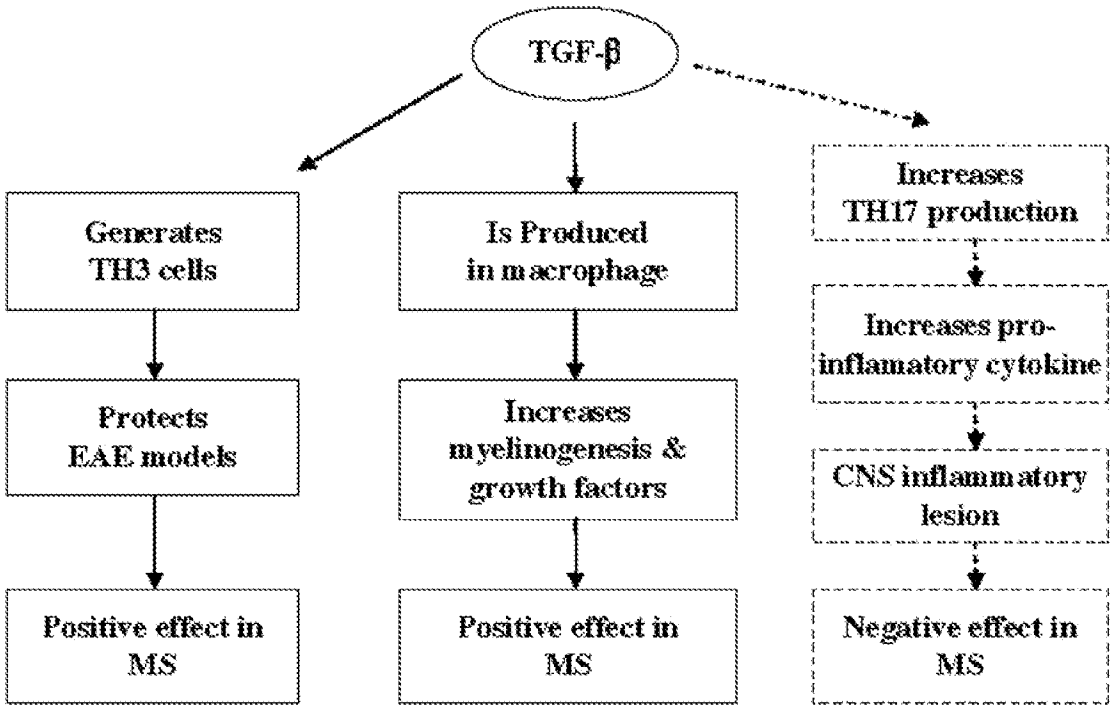

TGF-β
Generates TH3 cells
Protects EAE models
Positive effect in MS
Is Produced in macrophage
Increases myelinogenesis & growth factors
Positive effect in MS
Increases TH17 production
Increases pro-inflamatory cytokine
CNS inflammatory lesion
Negative effect in MS

FIGURE 5

Figure 5A

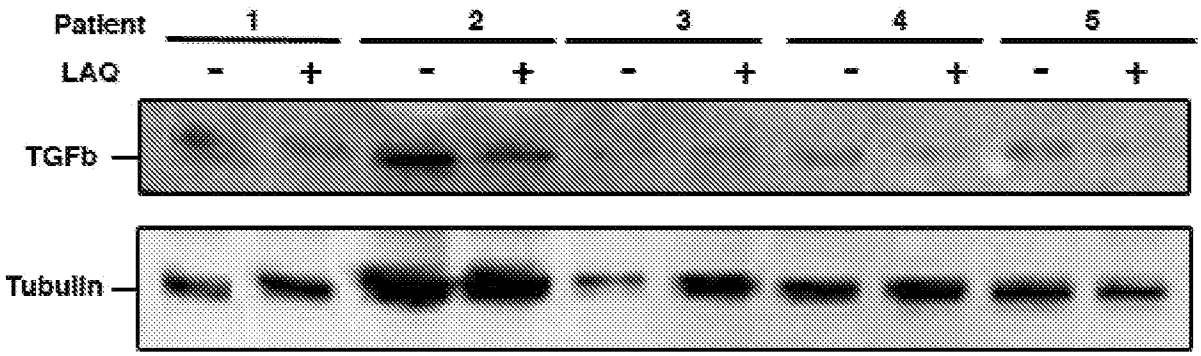


Figure 5B

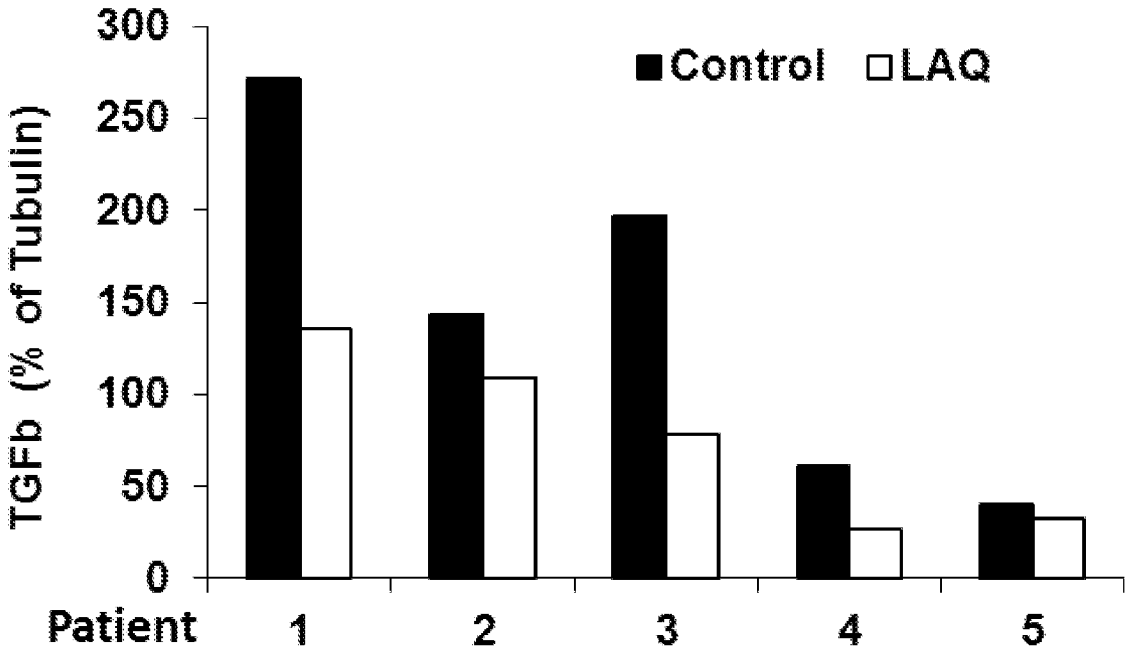


Figure 5C

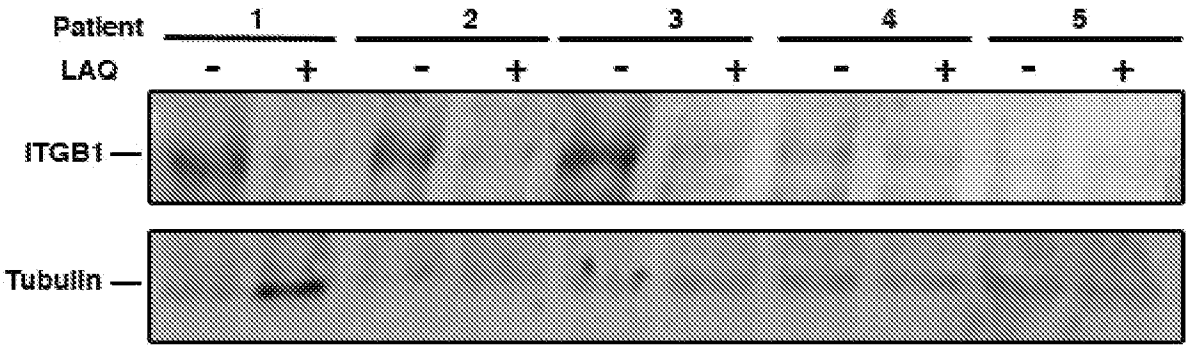


Figure 5D

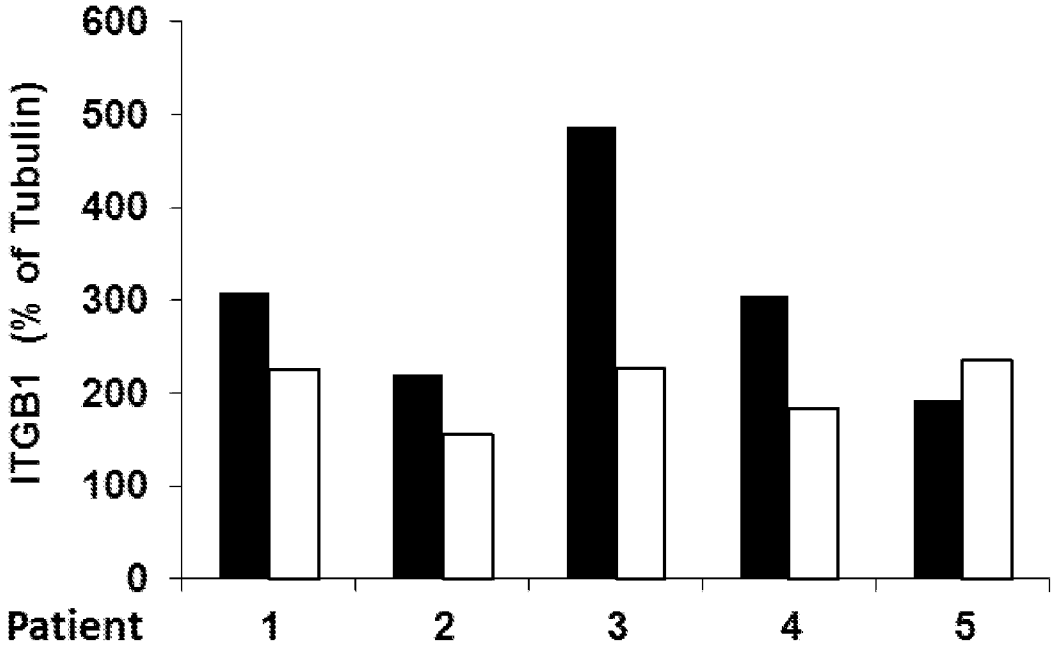


Figure 6B

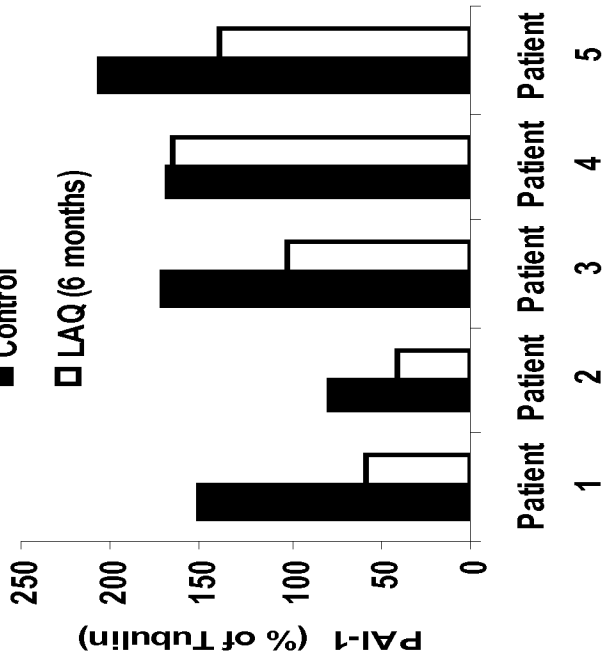


Figure 6A

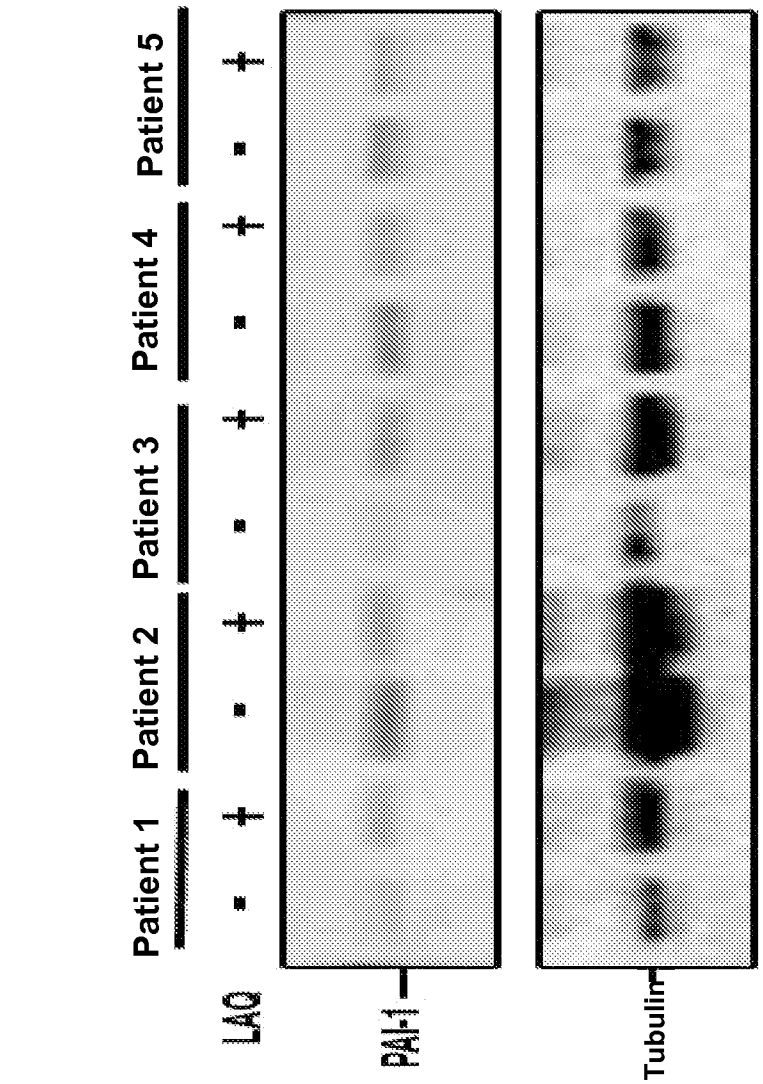


FIGURE 6

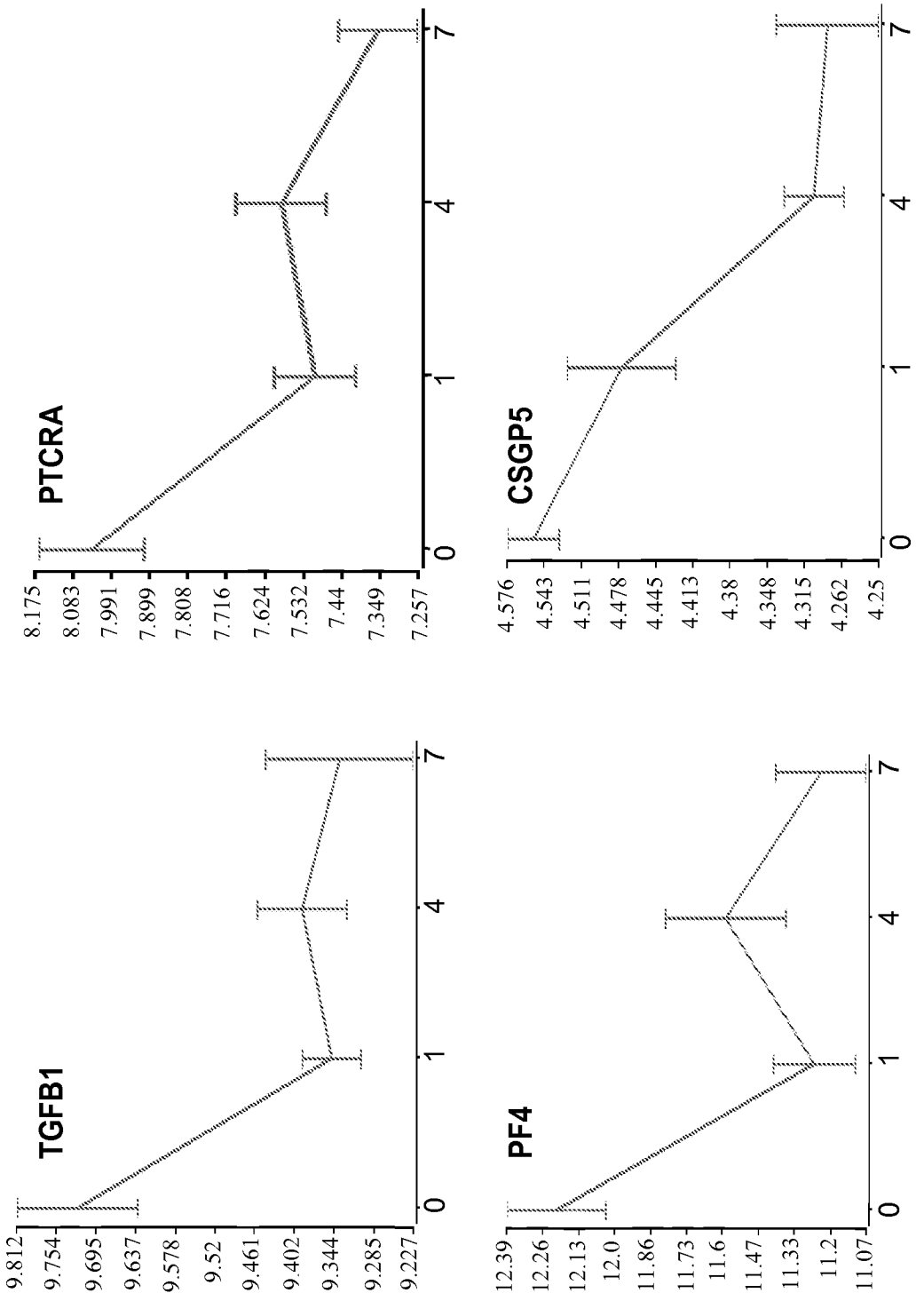

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7
CSGP5
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4.543
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4.445
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4.315
4.262
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TGFB1
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9.695
9.637
9.578
9.52
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9.402
9.344
9.285
9.227
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7
PF4
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12.26
12.13
12.0
11.86
11.73
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11.2
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7

FIGURE 7

SHEET 9/13

FIGURE 8

Figure 8A

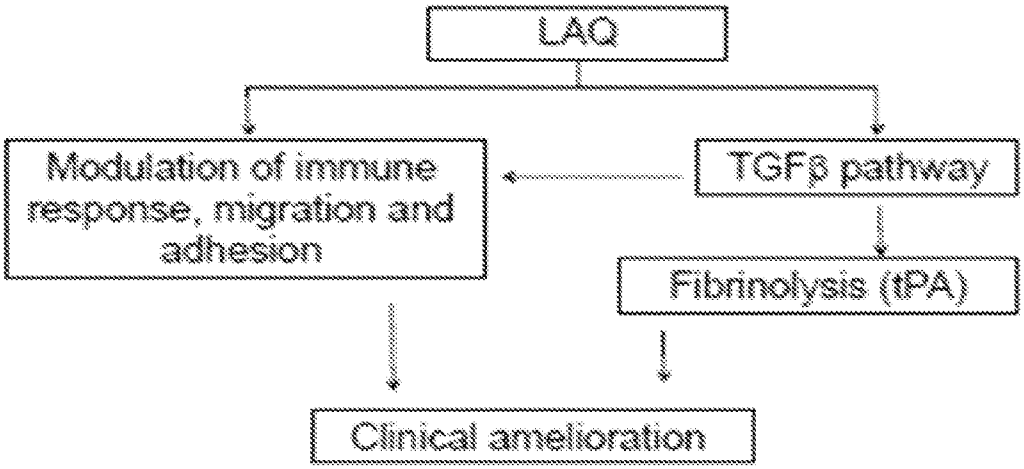


Figure 8B

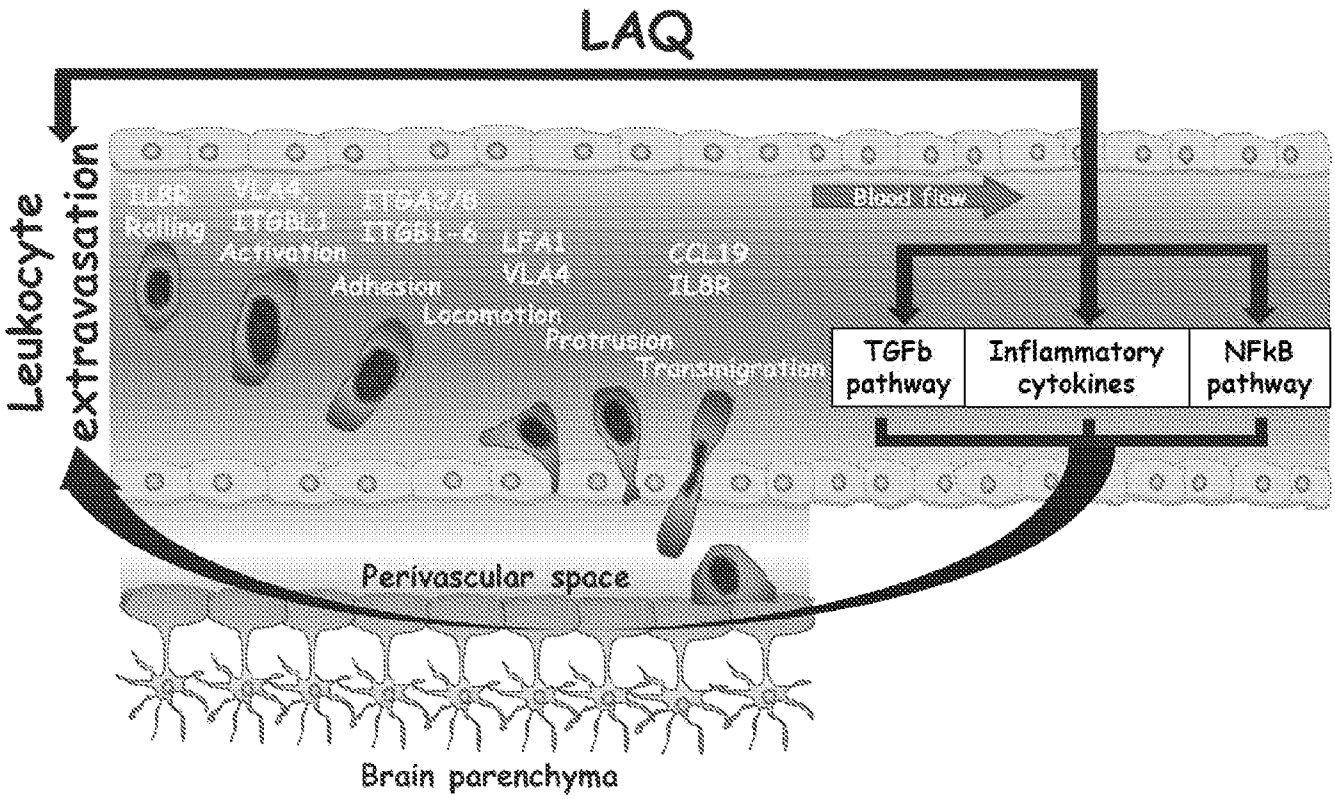
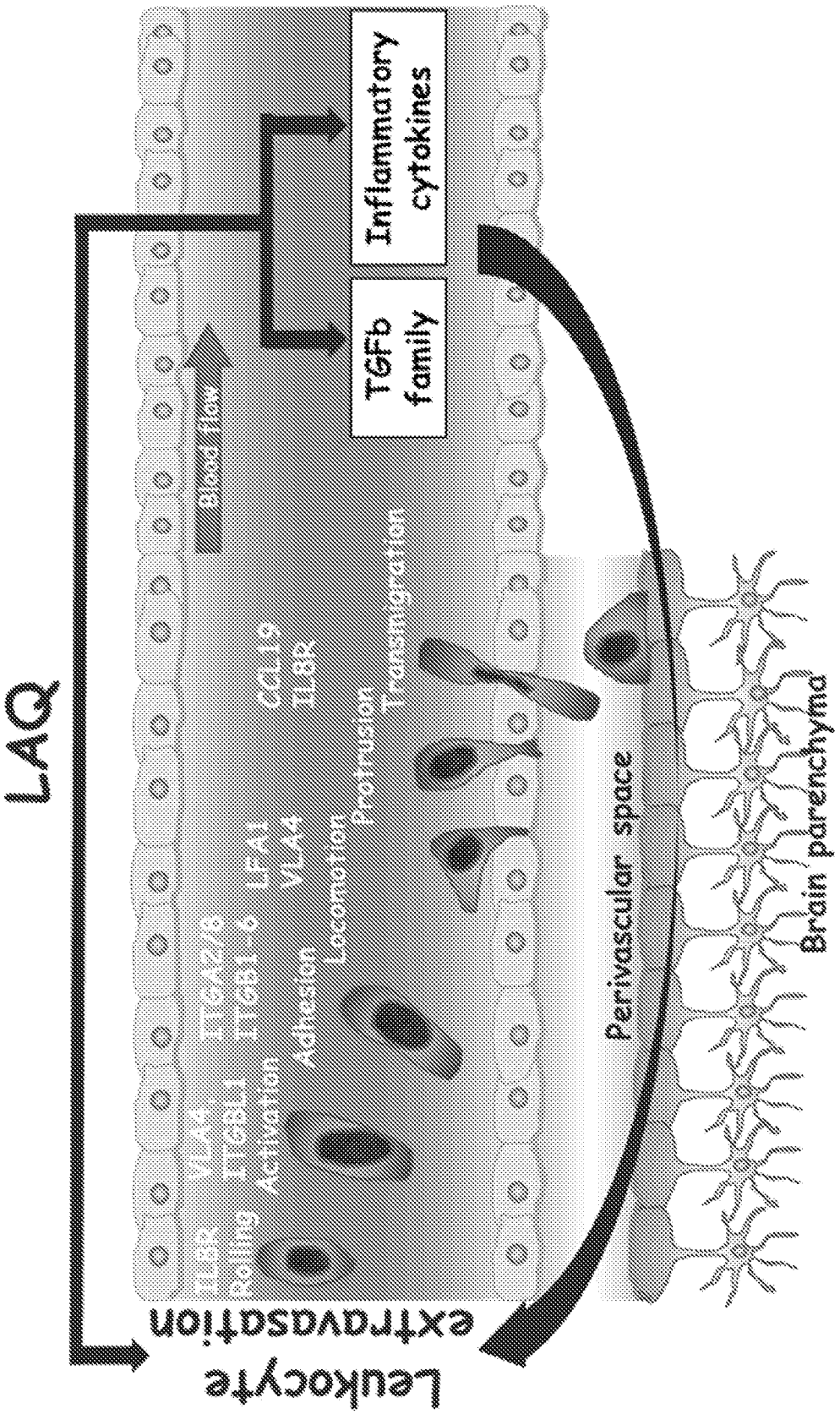


Figure 8C


LAQ
Leukocyte extravasation
Blood flow
Inflammatory cytokines
TGFb family
Perivascular space
Brain parenchyma
IL8R
Rolling
VLA4
ITGB1
Activation
ITGA4/6
ITGB1-6
Adhesion
LFA1
VLA4
Locomotion
CCL19
IL8R
Protrusion
Transmigration

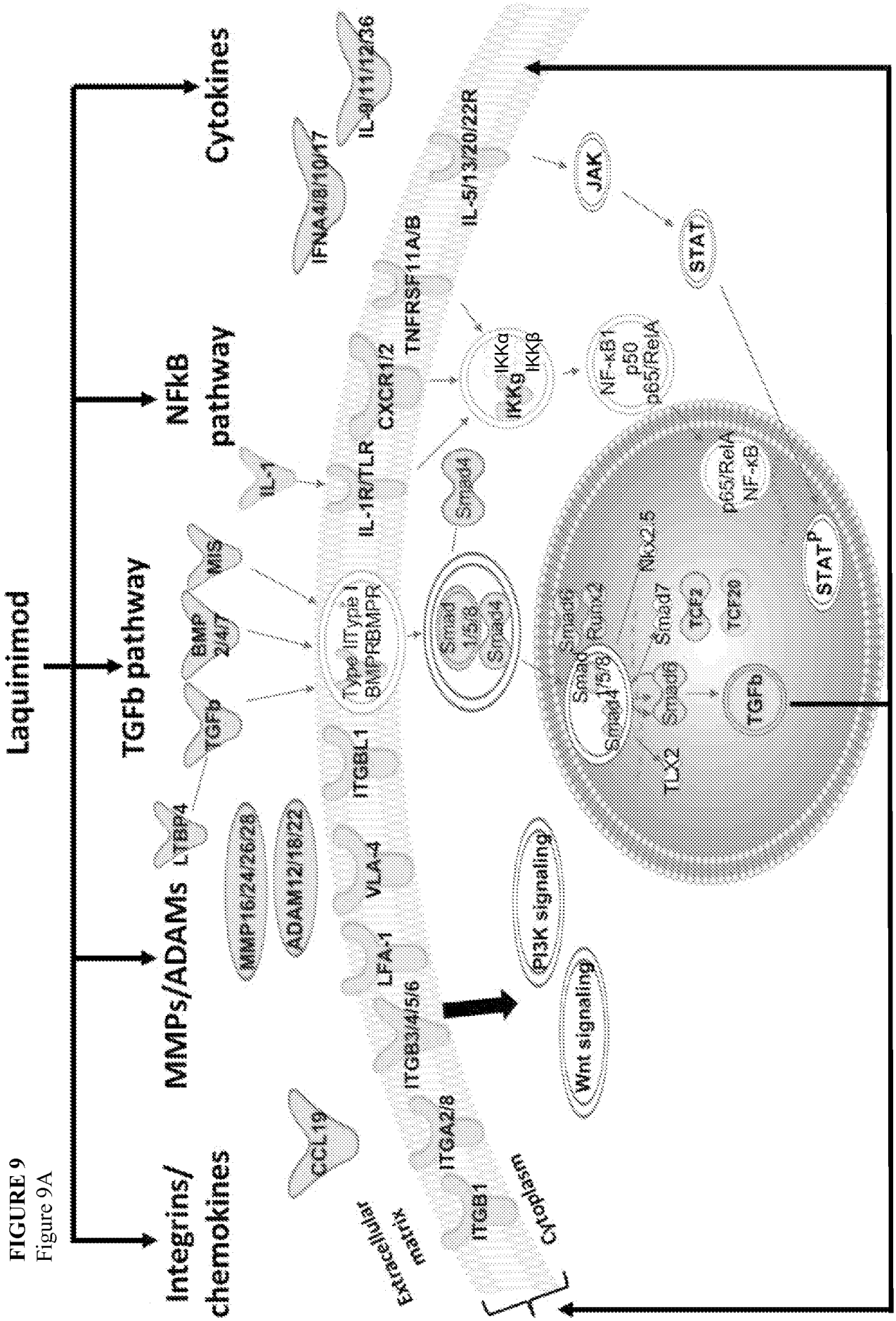
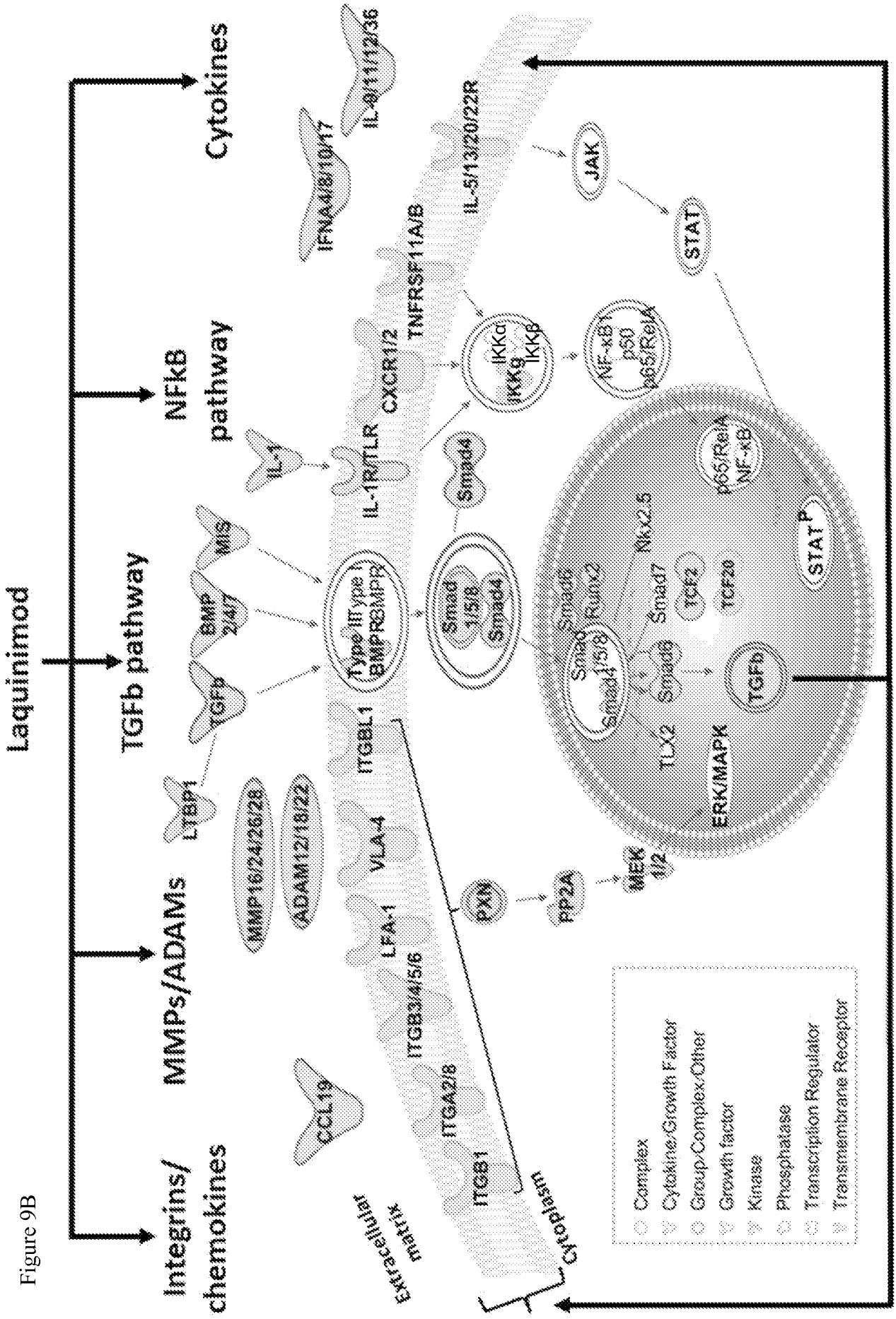


FIGURE 9
Figure 9A

Figure 9B


Laquinimod
Integrins/ chemokines
MMPs/ADAMs
TGFb pathway
NFkB pathway
Cytokines
CCL19
MMP16/24/26/28
ADAM12/18/22
LTBP1
TGFb
BMP 2/4/7
MIS
ITGBL1
VLA-4
LFA-1
ITGB3/4/5/6
ITGA2/8
ITGB1
Type II/Type I BMPR
IL-1
IL-1R/TLR
CXCR1/2
TNFRSF11A/B
IL-5/13/20/22R
IFNA4/8/10/17
IL-6/11/12/36
Smad4
Smad 1/5/8
Smad4
IKKα
IKKg
IKKβ
NF-κB1
p50
p65/RelA
JAK
STAT
PXN
PP2A
MEK 1/2
ERK/MAPK
Smad4
Smad1/5/8
Runx2
Nkx2.5
Smad7
TCF2
TCF20
TLX2
Smad6
TGFb
p65/RelA
NF-κB
STAT P
Cytoplasm
Complex
Cytokine/Growth Factor
Group/Complex/Other
Growth factor
Kinase
Phosphatase
Transcription Regulator
Transmembrane Receptor

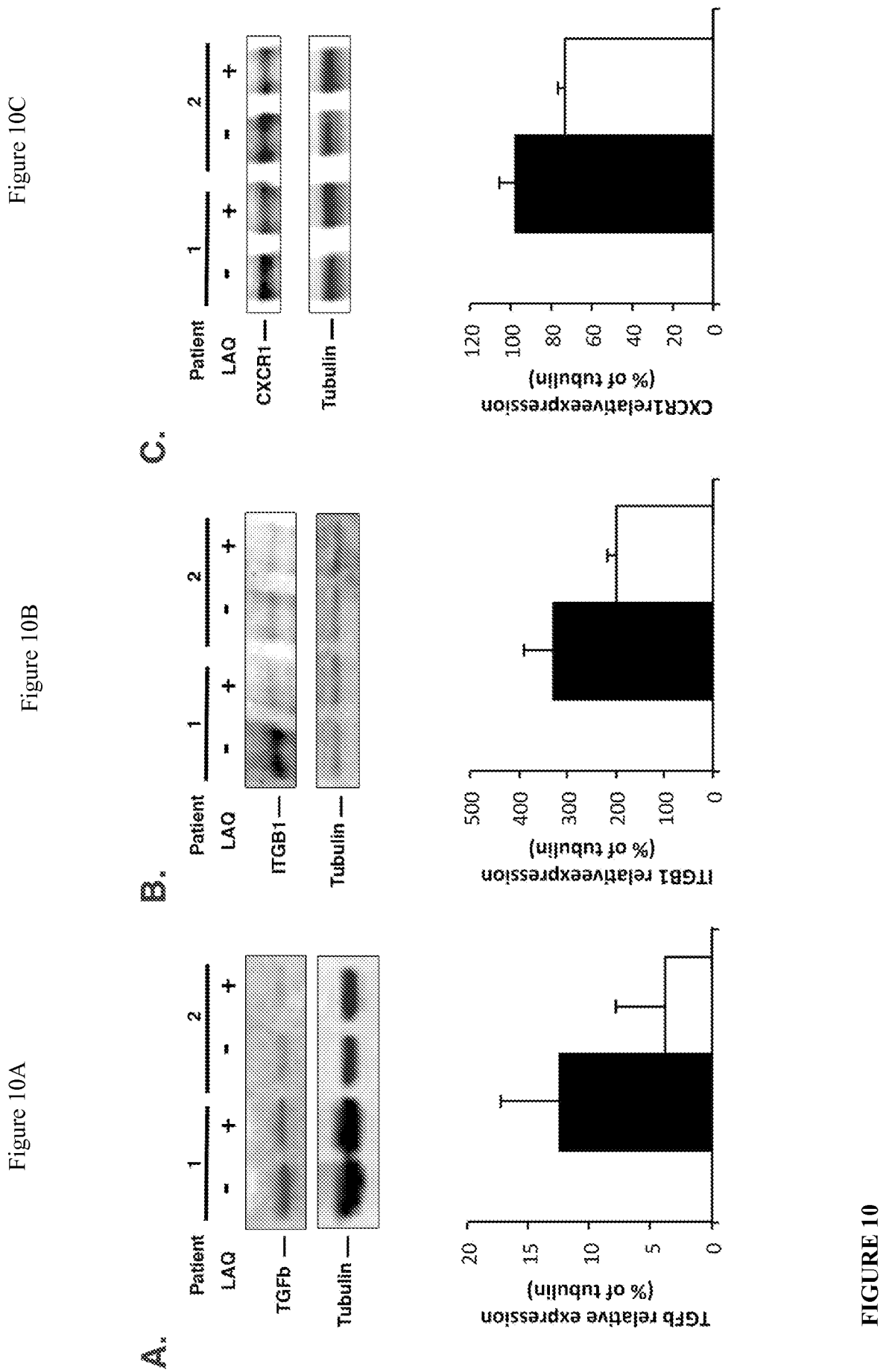


Figure 10A

Figure 10B

Figure 10C

FIGURE 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/55502

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/42; A61K 31/47; C12Q 1/68 (2014.01)
CPC - C07D 401/04, 401/12, 215/36, 215/22, 215/227; C12Q 1/6883; A61K 38/00, 1/6886
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)
IPC(8) Classification(s): A01N 43/42; A61K 31/47; C12Q 1/68; CPC Classification(s): C07D 401/04, 401/12; 215/36, 215/22, 215/227; C12Q 1/6883; A61K 38/00, 1/6886; USPC Classification(s): 514/312, 311, 299, 279, 277, 183.1; 546/155, 154, 152, 112, 26, 1; 435/6.16

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)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google; Google Scholar; Dialog ProQuest; Entrez Pubmed; 'response prediction,' 'multiple sclerosis,' 'inflammatory biomarker,' laquinimod, upregulation, suppression, expression, 'leukocyte migration,' 'unit dose,' packaging

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2013/0029916 A1 (GILGUN, Y et al.) January 13, 2013; abstract; paragraphs [0011], [0012], [0026], [0042], [0048], [0052], [0130], [0312], [0482], [0485]	50, 51, 53 --- 1-7, 14, 15, 46-49, 52
Y	WEST, MS et al. Profie Of Oral Laquinimod And Its Potential In The Treatment Of Multiple Sclerosis. Degenerative Neurology & Neuromuscular Disease. 21 July 2011, Vol. 1, pages 25-32; abstract; page 26, column 1, paragraph 1; page 26, column 1, paragraph 2; page 26, column 1, paragraph 4; page 27, column 1, paragraph 2; page 28, column 2, paragraph 2; page 30, column 1, paragagh 4.	1-7, 14, 15, 46-49, 52
A	US 2012/0039911 A1 (PARK, YW et al.) February 16, 2012; abstract	1-7, 14, 15, 46-53

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

* 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
25 November 2014 (25.11.2014)	11 DEC 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/55502

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

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

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

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

3. ☒ Claims Nos.: 8-13, 16-45
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.