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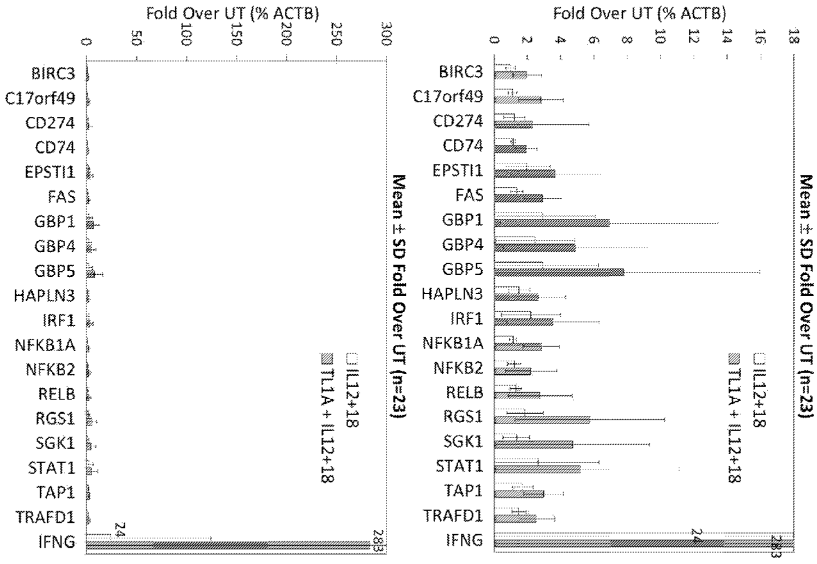
(54) **Title**: SYSTEMS, DEVICES AND METHODS FOR ANTI-TL1A THERAPY



(57) **Abstract**: The present invention relates to biomarker genes for diagnosing and treating diseases. Provided herein are systems and methods of diagnosing a disease in a patient based on the patient's expression levels of biomarker genes. Examples of the TL1A-associated disease include, but are not limited to, an inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), and fibrosis. Also provided herein are systems and methods of identifying a patient likely to be responsive to an anti-TL1A therapy, prescribing and/or administrating an anti-TL1A therapy to the patient based on the patient's expression levels of biomarker genes.

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SYSTEMS, DEVICES AND METHODS FOR ANTI-TL1A THERAPY

FIELD OF INVENTION

This invention relates to diagnosis and treatment of inflammatory and immune diseases. More specifically, this invention relates to systems, devices and methods for diagnosing and treating a disease that is susceptible to an anti-TL1A therapy.

BACKGROUND

All publications herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

TL1A activation is involved in pathogenesis of a variety of inflammatory and immune diseases. For example, genome-wide association studies (GWAS) have implicated TL1A in the pathogenesis of inflammatory bowel disease (IBD) such as Crohn's disease (CD). Evidence in preclinical mouse models also supports the role of TL1A in the pathogenesis of IBD. In addition, intestinal tissues from CD patients demonstrate increased expression of TL1A at sites of active disease. However, IBD is a heterogeneous disease, and previously, treatment of IBD patients has been by trial and error. While anti-TL1A therapy (e.g., treatment with an anti-TL1A antibody) is of help to some CD patients, not all patients will benefit from anti-TL1A therapy.

As such, there is a need of biomarkers, devices, systems, and methods for defining a biomarker signature for TL1A activation, for identifying patients who have most likely been inflicted by TL1A activation and will be most suitable for anti-TL1A therapy, and for guiding treatment options for these patients.

SUMMARY OF THE INVENTION

Various embodiments of the present invention provide a method of selecting a treatment for a subject. The method may comprise or may consist essentially of or may consist of: obtaining a sample from the subject, assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample, comparing the expression level to a reference value of expression level, and prescribing an anti-TL1A therapy to the subject if the subject has a high expression level relative to the reference value, or prescribing no anti-TL1A therapy to the subject if the subject does not have a high expression level relative to the reference value.

Various embodiments of the present invention provide a method of identifying a subject likely to be responsive to an anti-TL1A therapy. The method may comprise or may consist essentially of or may consist of: obtaining a sample from the subject, assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample, comparing the expression level to a reference value of expression level, and identifying the subject as likely to be responsive to an anti-TL1A therapy if the subject has a high expression level relative to the reference value, or identifying the subject as unlikely to be responsive to an anti-TL1A therapy if the subject does not have a high expression level relative to the reference value.

Various embodiments of the present invention provide a method of treating a subject with an anti-TL1A therapy. The method may comprise or may consist essentially of or may consist of: obtaining a sample from the subject, assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample, comparing the expression level to a reference value of expression level, and administering an anti-TL1A therapy to the subject if the subject has a high expression level relative to the reference value, or administering no anti-TL1A therapy to the subject if the subject does not have a high expression level relative to the reference value.

Various embodiments of the present invention provide a method of diagnosing a disease in a subject. The method may comprise or may consist essentially of or may consist of: obtaining a sample from the subject, assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample, comparing the expression level to a reference value of expression level, and diagnosing a TL1A-associated disease in the subject if the subject has a high expression level relative to the reference value, or diagnosing no TL1A-associated disease in the subject if the subject does not have a high expression level relative to the reference value.

Various embodiments of the present invention provide a method diagnosing susceptibility to a TL1A-associated disease in a subject. The method may comprise or may consist essentially of or may consist of: obtaining a sample from the subject, assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample, comparing the expression level to a reference value of expression level, and diagnosing susceptibility to a TL1A-associated disease in the subject if the subject has a high expression level relative to the reference value, or diagnosing no susceptibility to a TL1A-associated disease in the subject if the subject does not have a high expression level relative to the reference value.

Various embodiments of the present invention provide a method of treating a disease in a subject. The method may comprise or may consist essentially of or may consist of: administering an anti-TL1A therapy to the subject, thereby treating the disease, wherein the subject has a high expression level relative to a reference value of one or more biomarkers associated with TL1A signaling.

Various embodiments of the present invention provide a method for diagnosing a disease in a subject. The method may comprise or may consist essentially of or may consist of: obtaining a sample from a subject; assaying the expression level of one or more genes in the sample; comparing the expression level to a reference value of expression level of the one or more genes; and diagnosing a disease in the subject according to the relative difference between the expression level and the reference value. In some embodiments, the method further comprises diagnosing the disease in the subject if the subject has an expression level higher than the reference value, or not diagnosing the disease in the subject if the subject does not have an expression level higher than the reference value. In other embodiments, the method further comprises diagnosing the disease in the subject if the subject has an expression level lower than the reference value, or not diagnosing the disease in the subject if the subject does not have an expression level lower than the reference value. In various further embodiments, the method further comprises prescribing an anti-TL1A therapy to the subject if the subject is diagnosed with the disesae. In various further embodiments, the method further comprises administering an anti-TL1A therapy to the subject if the subject is diagnosed with the disease. In one embodiment, the disease is an IBD subtype, for example, an IBD subtype responsive to an anti-TL1A therapy.

Various embodiments of the present invention provide a method for diagnosing susceptibility to an IBD subtype in a subject. The method may comprise or may consist essentially of or may consist of: obtaining a sample from the subject; assaying the expression level of one or more genes in the sample; comparing the expression level to a reference value of expression level of the one or more genes; and diagnosing susceptibility to the IBD subtype in the subject if the subject has an expression level different from the reference value, or not diagnosing susceptibility to the IBD subtype in the subject if the subject does not have an expression level different from the reference value.

In various methods described herein, the one or more biomarkers or genes assayed may be those described in Table 1, Table 4, Table 5 and/or Table 6 herein. In various methods described herein, the TL1A-associated disease may include but are not limited to fibrosis, ulcerative colitis (UC), Crohn's disease (CD), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease, allergic lung inflammation, asthma, atherosclerosis, lupus, rheumatoid arthritis (RA), multiple sclerosis (MS), psoriasis, type 1 diabetes, lung carcinoma, colon carcinoma, leukemia, lymphoma, transplant rejection, graft versus host disease, or central nervous system injury. In various methods described herein, the IBD subtype may be characterized by being treatable with an anti-TL1A therapy, that is, an IBD subtype responsive to an anti-TL1A therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

Exemplary embodiments are illustrated in referenced figures. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

Figure 1 depicts genes as markers for activation by TL1A in accordance with various embodiments of the present invention. The same data of quantitative PCR results are shown on different X-axis scales in the top panel and the bottom panel. Bar graphs represent how many folds these biomarkers increase their expression levels over the untreated control (UT group), either after the cells are primed with IL12 and IL18 (Primed group), or after the cells are stimulated TL1A together with IL12 and IL18 (Stimulated group). For example, IFNG expression level increase about 24 folds over the untreated control after being primed with IL12 and IL18, and increase about 283 folds over the untreated control after being primed with IL12 and IL18 and further stimulated with TL1A. "% ACTB" means that the expression level of a biomarker is a value standardized to β-Actin (ACTB) expression level, which serves as an internal standard. The Primed value and the Stimulated value are divided by the UT value to obtain the increase fold of each gene.

Figure 2 depicts, in accordance with various embodiments of the present invention, effect of TL1A on IFNG mRNA. TL1A enhances IFN-γ Expression in CD4$^+$ T Cells.

Figure 3 depicts, in accordance with various embodiments of the present invention, intracellular IFN-γ in CD4$^+$ PBL. Only a small population (1.5-3%) of CD4$^+$ T cells upregulate IFN-γ production in response to TL1A. 1.5% of cell express IFN-γ in response to TL1A vs 8.5% in response to PMA/Ionomycin.

Figure 4 depicts experimental designs in accordance with various embodiments of the present invention. The strategy shown in the left panel looks for genes differentially regulated in response to IL12+18 as compared to IL12+18+TL1A. The strategy shown in the right panel looks for genes differentially regulated in response to TL1A between IFN-γ positive and IFN-γ negative cell populations.

Figure 5 depicts, in accordance with various embodiments of the present invention, capture of IFN-γ secreting cell population. Bivalent antibody binds to CD45 receptor on T cells and then capture IFN-γ protein. Protein is then detected by PE-anti-IFN-γ antibody.

Figure 6 depicts, in accordance with various embodiments of the present invention, CD4$^+$ IFN-sorted populations for new RNA-seq.

Figure 7 depicts, in accordance with various embodiments of the present invention, IBD samples are not activated by TL1A (%ACTB).

Figure 8 depicts, in accordance with various embodiments of the present invention, IBD samples are not activated by TL1A (%ACTB).

Figure 9 depicts, in accordance with various embodiments of the present invention, genes activated by IL12+18 (%ACTB).

Figure 10 depicts, in accordance with various embodiments of the present invention, genes activated by IL12+18 (%ACTB).

Figure 11 depicts, in accordance with various embodiments of the present invention, differential gene expression in UT IBD samples.

Figure 12 depicts, in accordance with various embodiments of the present invention, expression levels higher in IBD vs NL IL12+18-treated.

Figure 13 depicts, in accordance with various embodiments of the present invention, expression levels lower in IBD vs NL TL1A-treated.

DETAILED DESCRIPTION OF THE INVENTION

All references cited herein are incorporated by reference in their entirety as though fully set forth. Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Allen *et al.*, *Remington: The Science and Practice of Pharmacy 22nd ed.*, Pharmaceutical Press (September 15, 2012); Hornyak *et al.*, *Introduction to Nanoscience and Nanotechnology*, CRC Press (2008); Singleton and Sainsbury, *Dictionary of Microbiology and Molecular Biology 3rd ed., revised ed.*, J. Wiley & Sons (New York, NY 2006); Smith, *March's Advanced Organic Chemistry Reactions, Mechanisms and Structure 7th ed.*, J. Wiley & Sons (New York, NY 2013); Singleton, *Dictionary of DNA and Genome Technology 3rd ed.*, Wiley-Blackwell (November 28, 2012); and Green and Sambrook, *Molecular Cloning: A Laboratory Manual 4th ed.*, Cold Spring Harbor Laboratory Press (Cold Spring Harbor, NY 2012), provide one skilled in the art with a general guide to many of the terms used in the present application. For references on how to prepare antibodies, see Greenfield, *Antibodies A Laboratory Manual 2nd ed.*, Cold Spring Harbor Press (Cold Spring Harbor NY, 2013); Köhler and Milstein, *Derivation of specific antibody-producing tissue culture and tumor lines by cell fusion*, Eur. J. Immunol. 1976 Jul, 6(7):511-9; Queen and Selick, *Humanized immunoglobulins*, U. S. Patent No. 5,585,089 (1996 Dec); and Riechmann *et al.*, *Reshaping human antibodies for therapy*, Nature 1988 Mar 24, 332(6162):323-7.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Other features and advantages of the invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawings, which illustrate, by way of example, various features of embodiments of the invention. Indeed, the present invention is in no way limited to the methods and materials described.

"Subject" or "individual" or "patient" or "animal" or "mammal" refers to any subject, particularly a mammalian subject, for whom diagnosis, prognosis, treatment or therapy is desired. Mammalian subjects include, but are not limited to, humans; domestic animals; farm animals; zoo animals; sport animals; pet animals such as dogs, cats, guinea pigs, rabbits, rats, mice, horses, cattle, cows; primates such as apes, monkeys, orangutans, and chimpanzees; canids such as dogs and wolves; felids such as cats, lions, and tigers; equids such as horses, donkeys, and zebras; food animals such as cows, pigs, and sheep; ungulates such as deer and giraffes; rodents such as mice, rats, hamsters and guinea pigs; and so on. In certain embodiments, the mammal is a human subject. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be included within the scope of this term.

"Biological sample" or "Sample" as used herein means any biological material from which nucleic acids and/or proteins can be obtained. As non-limiting examples, the term encompasses whole blood, plasma, saliva, cheek swab, or other bodily fluid or tissue that contains nucleic acids and/or proteins.

"Treatment" and "treating," as used herein refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition, prevent the pathologic condition, pursue or obtain beneficial results, or lower the chances of the individual developing the condition even if the treatment is ultimately unsuccessful. Those in need of treatment include those already with the condition as well as those prone to have the condition or those in whom the condition is to be prevented.

"Beneficial results" may include, but are in no way limited to, lessening or alleviating the severity of the disease condition, preventing the disease condition from worsening, curing the disease condition, preventing the disease condition from developing, lowering the chances of a patient developing the disease condition and prolonging a patient's life or life expectancy. In some embodiments, the disease condition is a TL1A-associated disease.

"Patient outcome" refers to whether a patient's health improves or worsens as a result of treatment as well as whether a patient survives or dies as a result of treatment. As provided in this invention, prescribing and administering an appropriate treatment (e.g., an anti-TL1A therapy or not) according to the specific conditions of individual patients increases their chances of health improvement and/or survival.

"TL1A" as used herein is a TNF-like cytokine factor encoded by the gene TNFSF15. Examples of TL1A include mouse TL1A such as NCBI reference sequence NM_177371.3, rat TL1A such as NCBI reference sequence AF520787.1, and human TL1A such as NCBI reference sequence NM_005118, NM_001204344.1, among others.

"Anti-TL1A therapy", as used herein refers to therapeutic agents and methods that suppress TL1A gene expression, DR3 gene expression, or block the signaling of TL1A and DR3 (the receptor for TL1A) proteins. Examples of anti-TL1A therapy include, but are not limited to, an agent that specifically binds TL1A or DR3 and blocks TL1A-DR3 interaction, an anti-TL1A antibody blocking TL1A-DR3 signaling, an anti-DR3 antibody blocking TL1A-DR3 signaling, a soluble decoy DR3 polypeptide (e. g., a soluble DR3-Fc fusion protein), or a nucleic acid antagonist of TL1A or DR3, such as a ribozyme, aptamer or antisense molecule targeting TL1A or DR3, or a combination thereof.

As disclosed herein, the inventors discovered a TL1A-specific biomarker signature of 22 genes. In accordance with various embodiments herein, the invention includes devices, systems, and methods for stratifying patient population based on this biomarker signature to identify individuals most likely to been exposed in vivo to the pro-inflammatory effects of TL1A activation. As this particular population of patients would potentially benefit from an anti-TL1A therapy, for example, an anti-TL1A therapy may be prescribed or administrated to them. In another embodiment, by evaluating changes in the biomarker signature, one can monitor the progress and/or assess the effectiveness of an anti-TL1A therapy in a patient.

Methods of Diagnosis and Treatments

In one embodiment, the invention provides for a method of selecting a treatment for a subject. In one embodiment, the present invention provides a method of diagnosis and/or treatment by obtaining a sample from the subject, assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample, comparing the expression level to a reference value of expression level, and prescribing an anti-TL1A therapy to the subject if the subject has a high expression level relative to the reference value, or prescribing no anti-TL1A therapy to the subject if the subject does not have a high expression level relative to the reference value. In some embodiments, the method further comprises stimulating the sample with IL12, IL18, or TL1A, or a combination thereof, before assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample. In another embodiment, the one or more biomarkers associated with TL1A signaling is listed in Table 1, Table 4, Table 5 and/or Table 6 herein.

In one embodiment, the invention provides for a method of identifying a subject likely to be responsive to an anti-TL1A therapy. In one embodiment, the present invention provides a method of identifying a subject likely to be responsive to an anti-TL1A therapy by obtaining a sample from the subject, assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample, comparing the expression level to a reference value of expression level, and identifying the subject as likely to be responsive to an anti-TL1A therapy if the subject has a high expression level relative to the reference value, or identifying the subject as unlikely to be responsive to an anti-TL1A therapy if the subject does not have a high expression level relative to the reference value. In some embodiments, the method further comprises stimulating the sample with IL12, IL18, or TL1A, or a combination thereof, before assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample. In another embodiment, the one or more biomarkers associated with TL1A signaling is listed in Table 1, Table 4, Table 5 and/or Table 6 herein.

In another embodiment, the invention provides for a method of treating a subject with an anti-TL1A therapy. In one embodiment, the method includes obtaining a sample from the subject, assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample, comparing the expression level to a reference value of expression level, and administering an anti-TL1A therapy to the subject if the subject has a high expression level relative to the reference value, or administering no anti-TL1A therapy to the subject if the subject does not have a high expression level relative to the reference value. In some embodiments, the method further comprises stimulating the sample with IL12, IL18, or TL1A, or a combination thereof, before assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample. In another embodiment, the one or more biomarkers are described in Table 1, Table 4, Table 5 and/or Table 6 herein.

In another embodiment, the invention provides for a method of diagnosing a TL1A-associated disease in a subject. In another embodiment, the method comprises obtaining a sample from the subject, assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample, comparing the expression level to a reference value of expression level, and diagnosing a TL1A-associated disease in the subject if the subject has a high expression level relative to the reference value, or diagnosing no TL1A-associated disease in the subject if the subject does not have a high expression level relative to the reference value. In another embodiment, the one or more biomarkers are described in Table 1, Table 4, Table 5 and/or Table 6 herein.

In various embodiments, the invention provides for a method diagnosing susceptibility to a TL1A-associated disease in a subject. In one embodiment, the method comprises: obtaining a sample from the subject, assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample, comparing the expression level to a reference value of expression level, and diagnosing susceptibility to a TL1A-associated disease in the subject if the subject has a high expression level relative to the reference value, or diagnosing no susceptibility to a TL1A-associated disease in the subject if the subject does not have a high expression level relative to the reference value. In another embodiment, the one or more biomarkers associated with TL1A signaling is described in Table 1, Table 4, Table 5 and/or Table 6 herein. In another embodiment, the TL1A-associated disease includes fibrosis. In another embodiment, the TL1A-asssociated disease includes Inflammatory Bowel Disease (IBD).

In various embodiments, the invention provides a method of treating a disease in a subject. In one embodiment, the method comprises: administering an anti-TL1A therapy to the subject, thereby treating the disease, wherein the subject has a high expression level relative to a reference value of one or more biomarkers associated with TL1A signaling. In another embodiment, the one or more biomarkers are described in Table 1, Table 4, Table 5 and/or Table 6 herein.

In various embodiments, the invention provides for a method of diagnosing an IBD subtype in a subject. In one embodiment, the method comprises: obtaining a sample from the subject; assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample; comparing the expression level to a reference value of expression level; and diagnosing the IBD subtype in the subject if the subject has a high expression level relative to the reference value, or not diagnosing the IBD subtype in the subject if the subject does not have a high expression level relative to the reference value. In some embodiments, the method further comprises stimulating the sample with IL12, IL18, or TL1A, or a combination thereof, before assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample. In another embodiment, the one or more biomarkers are described in Table 1, Table 4, Table 5 and/or Table 6 herein. In one embodiment, the IBD subtype is characterized by being treatable with an anti-TL1A therapy.

In various embodiments, the invention provides for a method for diagnosing a disease in a subject. In one embodiment, the method comprises: obtaining a sample from a subject; assaying the expression level of one or more genes listed in Table 1, Table 4, Table 5 and/or

Table 6 herein in the sample; comparing the expression level to a reference value of expression level of the one or more genes; and diagnosing a disease in the subject according to the relative difference between the expression level and the reference value. In some embodiments, the method further comprises stimulating the sample with IL12, IL18, or TL1A, or a combination thereof, before assaying the expression level of one or more genes in the sample. In some embodiments, the method further comprises diagnosing the disease in the subject if the subject has an expression level higher than the reference value, or not diagnosing the disease in the subject if the subject does not have an expression level higher than the reference value. In other embodiments, the method further comprises diagnosing the disease in the subject if the subject has an expression level lower than the reference value, or not diagnosing the disease in the subject if the subject does not have an expression level lower than the reference value. In various further embodiments, the method further comprises prescribing an anti-TL1A therapy to the subject if the subject is diagnosed with the disease. In various further embodiments, the method further comprises administering an anti-TL1A therapy to the subject if the subject is diagnosed with the disease.

In various embodiments, the disease is a TL1A-associated disease. In various embodiments, the disease is fibrosis, Crohn's disease (CD), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease, allergic lung inflammation, asthma, atherosclerosis, lupus, rheumatoid arthritis (RA), multiple sclerosis (MS), psoriasis, type 1 diabetes, lung carcinoma, colon carcinoma, leukemia, lymphoma, transplant rejection, graft versus host disease, or central nervous system injury. In various embodiments, the disease is a subtype of a disease, such as an IBD subtype responsive to an anti-TL1A therapy.

In various embodiments, the method comprises diagnosing the disease in the subject if the subject has an expression profile different from a reference profile, or not diagnosing the disease in the subject if the subject does not have an expression profile different from a reference profile. In accordance with the present invention, the expression profile may comprise a plurality of gene expression levels, in which some gene expression levels may be higher and other gene expression levels may be lower than the reference profile.

In various embodiments, the invention provides for a method of diagnosing susceptibility to an IBD subtype in a subject. In one embodiment, the method comprises: obtaining a sample from the subject; assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample; comparing the expression level to a reference value of expression level; and diagnosing susceptibility to the IBD subtype in the subject if the subject has a high expression level relative to the reference value, or diagnosing no susceptibility to the IBD subtype in the subject if the subject does not have a high expression level relative to the reference value. In another embodiment, the one or more biomarkers are described in Table 1, Table 4, Table 5 and/or Table 6 herein. In one embodiment, the IBD subtype is characterized by being treatable with an anti-TL1A therapy.

In various embodiments, the invention provides for a method for diagnosing susceptibility to an IBD subtype in a subject. In one embodiment, the method comprises: obtaining a sample from the subject; assaying the expression level of one or more genes in the sample; comparing the expression level to a reference value of expression level of the one or more genes; and diagnosing susceptibility to the IBD subtype in the subject if the subject has an expression level different from the reference value, or not diagnosing susceptibility to the IBD subtype in the subject if the subject does not have an expression level different from the reference value. In various embodiments, the one or more genes is listed in Table 1, Table 4, Table 5 and/or Table 6 herein. In various embodiments, the IBD subtype is a subtype responsive to an anti-TL1A therapy.

In some embodiments, assaying the expression level of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6 herein in the sample comprise assaying at least two, three, four, or five genes listed in Table 1, Table 4, Table 5 and/or Table 6 herien. In other embodiments, assaying the expression level of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6 herein in the sample comprise assaying all of genes listed in Table 1, Table 4, Table 5 and/or Table 6 herein. In another embodiment, assaying the expression level of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6 herein in the sample comprise assaying any number (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55) of genes listed in Table 1, Table 4, Table 5 and/or Table 6 herein. In various embodiments, the methods described herein comprise assaying the expression level of one or more genes listed Table 6.

In various embodiments, the methods described herein comprise assaying the expression level of one or more genes selected from the group consisting of BIRC3, C17orf49, CCL20,

CSF2, CD274, CD74, EPSTI1, FAS, GBP1, GBP4, GBP5, HAPLN3, IFNG, IRF1, NFKBIA, NFKB2, RELB, RGS1, SGK1, STAT1, TAP1, and TRAFD1. In various embodiments, the methods described herein comprise assaying the expression level of one or more genes selected from the group consisting of BATF, CCL20, CD274, CD83, CDKN1A, CHAC1, CSF2, DUSP5, FEZ1, GADD45G, HMSD, IFNG, IL22, IL26, IL4I1, IRF8, LTA, MFSD2A, MYO1B, NFKBIA, RPL21, SGK1, TNFRSF18, TNFRSF4, TRAF4, and XIST.

Subject

In accordance with various embodiments herein, the subject can be human, monkey, ape, dog, cat, cow, horse, goat, pig, rabbit, mouse or rat. In one embodiment, the subject has a symptom of a TL1A-associated disease, is suspected of having a TL1A-associated disease, or is diagnosed with a TL1A-associated disease. In another embodiment, the subject has received, is receiving, or will receive an anti-TL1A therapy. In another embodiment, the subject has been, is being, or will be treated for a TL1A-associated disease. In another embodiment, the subject is in complete or partial remission, or has a recurrence of a TL1A-associated disease. In one embodiment, the subject has a symptom of an IBD subtype. In another embodiment, the subject is suspected of having an IBD subtype. In some embodiments, the IBD subtype is a subtype responsive to an anti-TL1A therapy.

Sample

In one embodiment, the sample comprises a T cell, $CD4^+$ T cell, $CD8^+$ T cell, $CD56^+$ T cell, $CD45R0^+$ T cell, $CD45RA^+$ T cell, NK cell, peripheral blood mononuclear cell (PBMC), or peripheral blood lymphocyte (PBL), or a combination thereof. In various embodiments, the sample is a cell, tissue, or body fluid. In various embodiments, the sample can be serum, urine, blood, plasma, saliva, semen, lymph, or a combination thereof. In various embodiments, the sample can be obtained before, during, or after a treatment of TL1A-associated disease. In various embodiments, the sample can be obtained before, during, or after an anti-TL1A therapy.

TL1A-associated disease

In accordance with various embodiments herein, the TL1A-associated disease is fibrosis, Crohn’s disease (CD), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease, allergic lung inflammation, asthma, atherosclerosis, lupus, rheumatoid arthritis (RA), multiple sclerosis (MS), psoriasis, type 1 diabetes, lung carcinoma, colon carcinoma, leukemia, lymphoma, transplant rejection, graft versus host disease, or central nervous system injury.

Examples of "TL1A-associated diseases" include, but are not limited to, fibrosis, Crohn's disease (CD), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease, allergic lung inflammation, asthma, atherosclerosis, lupus, rheumatoid arthritis (RA), multiple sclerosis (MS), psoriasis, type 1 diabetes, lung carcinoma, colon carcinoma, leukemia, lymphoma, transplant rejection, graft versus host disease, or central nervous system injury.

IBD includes several forms of inflammatory diseases and conditions affecting various parts of the gastrointestinal (GI) tract, such as the colon and small intestine. Examples of IBD include, but are not limited to, Crohn's disease (CD), ulcerative colitis (UC), other forms of colitis such as collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behçet's disease, and indeterminate colitis, among others. Crohn's disease (CD) and ulcerative colitis (UC) are two main forms of IBD. Hallmarks of IBD can include inflammation of the digestive tract in compartments of the epithelial mucosa or transmural lesions in the bowel wall.

Expression Level Assay – RNA

In various embodiments, assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample comprises assaying an mRNA level. In various embodiments, assaying an mRNA level comprises using RNA sequencing, northern blot, in situ hybridization, hybridization array, serial analysis of gene expression (SAGE), reverse transcription PCR, real-time PCR, real-time reverse transcription PCR, or quantitative PCR, or a combination thereof.

In various embodiments, assaying an mRNA level comprises contacting the sample with a polynucleotide probe capable of specifically hybridizing to mRNA of one or more biomarkers associated with TL1A signaling and thereby forming a probe-target hybridization complex.

Hybridization-based RNA assays include, but are not limited to, traditional "direct probe" methods such as, northern blot or *in situ* hybridization (*e.g.,* Angerer (1987) *Meth. Enzymol* 152: 649). The methods can be used in a wide variety of formats including, but not limited to, substrate (e.g. membrane or glass) bound methods or array-based approaches. In a typical *in situ* hybridization assay, cells are fixed to a solid support, typically a glass slide. If a nucleic acid is to be probed, the cells are typically denatured with heat or alkali. The cells are then contacted with a hybridization solution at a moderate temperature to permit annealing of labeled probes specific to the nucleic acid sequence encoding the protein. The targets (*e.g.,* cells) are then typically washed at a predetermined stringency or at an increasing stringency until an appropriate signal to noise ratio is obtained. The probes are typically labeled, *e.g.,* with radioisotopes or fluorescent reporters. Preferred probes are sufficiently long so as to specifically hybridize with the target nucleic acid(s) under stringent conditions. The preferred size range is from about 200 bases to about 1000 bases. Hybridization protocols suitable for use with the methods of the invention are described, *e.g.,* in Albertson (1984) *EMBO J.* 3: 1227-1234; Pinkel (1988) *Proc. Natl. Acad. Sci. USA* 85: 9138-9142; EPO Pub. No. 430,402; *Methods in Molecular Biology*, Vol. 33: *In situ* Hybridization Protocols, Choo, ed., Humana Press, Totowa, N.J. (1994), Pinkel, *et al.* (1998) *Nature Genetics* 20: 207-211, and/or Kallioniemi (1992) *Proc. Natl Acad Sci USA* 89:5321-5325 (1992). In some applications, it is necessary to block the hybridization capacity of repetitive sequences. Thus, in some embodiments, tRNA, human genomic DNA, or Cot-I DNA is used to block non-specific hybridization.

In various embodiments, assaying an mRNA level comprises contacting the sample with one or more polynucleotide primers capable of specifically hybridizing to mRNAs of genes listed in Table 1, Table 4, Table 5 and/or Table 6, forming a primer-template hybridization complex, and performing a PCR reaction. In some embodiments, the one or more polynucleotide primers are primers listed in Table 2. In other embodiments, the one or more polynucleotide primers comprises about 15-45, 20-40, or 25-35 bp sequences that are identical (for forward primers) or complementary (for reverse primers) to sequences of genes listed in Table 1, Table 4, Table 5 and/or Table 6. As a non-liming example, the one or more polynucleotide primers for INFG (e.g., NM_000619.2 with 1240 bp) can comprise sequences that are identical (for forward primers) or complementary (for reverse primers) to INFG's bp 1-20, 5-25, 10-30, 15-35, 20-40, 25-45, 30-50, so on and so forth, until the end of INFG, 1201-1220, 1205-25, 1210-1230, 1215-1235, 1220-1240. While not listed here exhaustively because of the space, all these polynucleotide primers for INFG and other genes listed in Table 1, Table 4, Table 5 and/or Table 6 can be used in the present invention. In various embodiments, the one or more polynucleotide primers are labeled with radioisotopes or fluorescent molecules. As the labeled primers emit radio or fluorescent signals, the PCR products containing the labeled primers can be detected and analyzed with a variety of imaging equipment.

Methods of "quantitative" amplification are well known to those of skill in the art. For example, quantitative PCR involves simultaneously co-amplifying a known quantity of a control sequence using the same primers. This provides an internal standard that may be used to calibrate the PCR reaction. Detailed protocols for quantitative PCR are provided in Innis, *et al.* (1990) PCR Protocols, *A Guide to Methods and Applications*, Academic Press, Inc. N.Y.). Measurement of DNA copy number at microsatellite loci using quantitative PCR anlaysis is described in Ginzonger, *et al.* (2000) *Cancer Research* 60:5405-5409. The known nucleic acid sequence for the genes is sufficient to enable one of skill in the art to routinely select primers to amplify any portion of the gene. Fluorogenic quantitative PCR may also be used in the methods of the invention. In fluorogenic quantitative PCR, quantitation is based on amount of fluorescence signals, *e.g.,* TaqMan and sybr green. Other suitable amplification methods include, but are not limited to, ligase chain reaction (LCR) (see Wu and Wallace (1989) *Genomics* 4: 560, Landegren, *et al.* (1988) *Science* 241:1077, and Barringer et al. (1990) *Gene* 89: 117), transcription amplification (Kwoh, *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86: 1173), self-sustained sequence replication (Guatelli, *et al.* (1990) *Proc. Nat. Acad. Sci. USA* 87: 1874), dot PCR, and linker adapter PCR, *etc.*

Expression Level Assay – Protein

In various embodiments, assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample comprises assaying a protein level. In various embodiments, assaying a protein level comprises using western blot, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, or mass spectrometry, or a combination thereof.

In various embodiments, assaying a protein level comprises contacting the sample with antibodies capable of specifically binding to proteins of genes listed in Table 1, Table 4, Table 5 and/or Table 6 and thereby forming antigen-antibody complexes. In the methods and assays of the invention, the expression levels of proteins encoded by biomarker genes listed in Table 1, Table 4, Table 5 and/or Table 6, or fragments or variants thereof can be determined using antibodies specific for those individual proteins or fragments or variants thereof and detecting immunospecific binding of each antibody to its respective cognate biomarker protein.

Antibodies, both polyclonal and monoclonal, can be produced by a skilled artisan either by themselves using well known methods or they can be manufactured by service providers who specialize making antibodies based on known protein sequences. In the present invention, the protein sequences of biomarker gens are known and thus production of antibodies against them is a matter of routine.

For example, production of monoclonal antibodies can be performed using the traditional hybridoma method by first immunizing mice with an antigen which may be an isolated protein of choice or fragment thereof (for example, a protein encode by a biomarker gene listed in Table 1, Table 4, Table 5 and/or Table 6, or a fragment thereof or a variant thereof) and making hybridoma cell lines that each produce a specific monoclonal antibody. The antibodies secreted by the different clones are then assayed for their ability to bind to the antigen using, e.g., ELISA or Antigen Microarray Assay, or immuno-dot blot techniques. The antibodies that are most specific for the detection of the protein of interest can be selected using routine methods and using the antigen used for immunization and other antigens as controls. The antibody that most specifically detects the desired antigen and protein and no other antigens or proteins are selected for the processes, assays and methods described herein. The best clones can then be grown indefinitely in a suitable cell culture medium. They can also be injected into mice (in the peritoneal cavity, surrounding the gut) where they produce an antibody-rich ascites fluid from which the antibodies can be isolated and purified. The antibodies can be purified using techniques that are well known to one of ordinary skill in the art.

Any suitable immunoassay method may be utilized, including those which are commercially available, to determine the expression level of a biomarker protein or a variant thereof assayed according to the invention. Extensive discussion of the known immunoassay techniques is not required here since these are known to those of skill in the art. Typical suitable immunoassay techniques include sandwich enzyme-linked immunoassays (ELISA), radioimmunoassays (RIA), competitive binding assays, homogeneous assays, heterogeneous assays, etc.

For example, in the assays of the invention, “sandwich-type” assay formats can be used. An alternative technique is the “competitive-type” assay. In a competitive assay, the labeled probe is generally conjugated with a molecule that is identical to, or an analog of, the analyte. Thus, the labeled probe competes with the analyte of interest for the available receptive material.

Competitive assays are typically used for detection of analytes such as haptens, each hapten being monovalent and capable of binding only one antibody molecule.

The antibodies can be labeled. In some embodiments, the detection antibody is labeled by covalently linking to an enzyme, label with a fluorescent compound or metal, label with a chemiluminescent compound. For example, the detection antibody can be labeled with catalase and the conversion uses a colorimetric substrate composition comprises potassium iodide, hydrogen peroxide and sodium thiosulphate; the enzyme can be alcohol dehydrogenase and the conversion uses a colorimetric substrate composition comprises an alcohol, a pH indicator and a pH buffer, wherein the pH indicator is neutral red and the pH buffer is glycine-sodium hydroxide; the enzyme can also be hypoxanthine oxidase and the conversion uses a colorimetric substrate composition comprises xanthine, a tetrazolium salt and 4,5-dihydroxy-1,3-benzene disulphonic acid. In one embodiment, the detection antibody is labeled by covalently linking to an enzyme, label with a fluorescent compound or metal, or label with a chemiluminescent compound.

Direct and indirect labels can be used in immunoassays. A direct label can be defined as an entity, which in its natural state, is visible either to the naked eye or with the aid of an optical filter and/or applied stimulation, e.g., ultraviolet light, to promote fluorescence. Examples of colored labels which can be used include metallic sol particles, gold sol particles, dye sol particles, dyed latex particles or dyes encapsulated in liposomes. Other direct labels include radionuclides and fluorescent or luminescent moieties. Indirect labels such as enzymes can also be used according to the invention. Various enzymes are known for use as labels such as, for example, alkaline phosphatase, horseradish peroxidase, lysozyme, glucose-6-phosphate dehydrogenase, lactate dehydrogenase and urease.

The antibody can be attached to a surface. Examples of useful surfaces on which the antibody can be attached for the purposes of detecting the desired antigen include nitrocellulose, PVDF, polystyrene, and nylon.

In some embodiments of the processes, assays and methods described herein, detecting the level of antibodies reactive to a biomarker protein or a variant thereof includes contacting the sample from the cancer patient with an antibody or a fragment thereof that specifically binds a biomarker protein or a variant thereof, forming an antibody-protein complex between the antibody and the biomarker protein or a variant thereof present in the sample, washing the sample to remove the unbound antibody, adding a detection antibody that is labeled and is reactive to the antibody bound to the biomarker protein or a variant thereof in the sample, washing to remove the unbound labeled detection antibody and converting the label to a detectable signal, wherein the detectable signal is indicative of the level of biomarker protein or a variant thereof in the sample from the patient. In some embodiments, the effector component is a detectable moiety selected from the group consisting of a fluorescent label, a radioactive compound, an enzyme, a substrate, an epitope tag, electron-dense reagent, biotin, digonigenin, hapten and a combination thereof. In some embodiments, the detection antibody is labeled by covalently linking to an enzyme, labeled with a fluorescent compound or metal, labeled with a chemiluminescent compound. The level of biomarker protein may be obtained by assaying a light scattering intensity resulting from the formation of an antibody-protein complex formed by a reaction of biomarker protein in the sample with the antibody, wherein the light scattering intensity of at least 10% above a control light scattering intensity indicates the likelihood of chemotherapy resistance.

Reference Value of Expression Level

In various embodiments, the reference value of expression level is the median or mean expression level from a population of subjects who have no TL1A-associated disease. In one embodiment, the reference value of expression level is the median or mean expression level from a population of subjects who have no IBD. In various embodiments, the reference value of expression level is the median or mean expression level from a population of subjects who are unlikely to be responsive to an anti-TL1A therapy. In various embodiments, the reference value of expression level is the median or mean expression level from a population of subjects who are not responsive to an anti-TL1A therapy. In additional embodiments, the reference value is the expression level of a biomarker gene or a variant thereof in a sample obtained from the subject at a different (for example, an earlier) time point, such as during diagnosis, before treatment, during treatment, after treatment or a combination thereof.

Various statistical methods, for example, a two-tailed student t-test with unequal variation, may be used to measure the differences in expression levels of a biomarker gene between the subject's sample and a control sample from a normal/healthy individual, or a reference value of expression level generate by computer algorithm pooling many control samples, as described herein. A significant difference may be achieved where the p value is equal to or less than 0.05.

In various embodiments, the expression level of a biomarker gene or a variant thereof in the subject as compared to the reference value is higher by at least or about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100%. In various embodiments, the expression level of a biomarker gene or a variant thereof in the subject as compared to the reference value is increased by at least or about 1.1-fold, 1.2-fold, 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2-fold, 2.1-fold, 2.2-fold, 2.3-fold, 2.4-fold, 2.5-fold, 2.6-fold, 2.7-fold, 2.8-fold, 2.9-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold or 10-fold, 15-fold, 20-fold, 25-fold, 30-fold, 35-fold, 40-fold, 45-fold, 50-fold, 55-fold, 60-fold, 65-fold, 70-fold, 75-fold, 80-fold, 85-fold, 90-fold, 95-fold, or 100-fold.

Anti-TL1A Therapy

In various embodiments, the anti-TL1A therapy comprises an agent that specifically binds TL1A or DR3 and blocks TL1A-DR3 interaction. In one embodiment, the anti-TL1A therapy comprises an anti-TL1A antibody or a fragment thereof, antagonistic anti-TL1A antibodies, or an isolated antigen-binding polypeptide that binds specifically to TL1A, or a combination thereof. In one embodiment, the anti-TL1A therapy comprises a soluble form of TL1A that specifically binds DR3. In one embodiment, the anti-TL1A therapy comprises an anti-DR3 antibody or a fragment thereof, antagonistic anti-DR3 antibodies, an isolated antigen-binding polypeptide that binds specifically to DR3, or a combination thereof. In one embodiment, the anti-TL1A therapy comprises a soluble form of DR3 that specifically binds TL1A. In one embodiment, the anti-TL1A therapy comprises a soluble decoy DR3 polypeptide, a polypeptide comprising a DR3 extracellular domain, a DR3-Fc protein, or a polypeptide comprising a DR3 pre-ligand assembly domain (a DR3-PLAD peptide), or a combination thereof. In one embodiment, the anti-TL1A therapy comprises a dominant negative DR3. In one embodiment, the anti-TL1A therapy comprises agents targeting TL1A or DR3 expression (e.g., ribozymes, aptamers and antisense nucleic acids), a nucleic acid antagonist of TL1A, or a nucleic acid antagonist of DR3), or a combination thereof. In one embodiment, the anti-TL1A therapy comprises GEP and GEP peptides including the peptide(s) denoted Atsttrin, Atsttrin-α variants, or a combination thereof.

The duration and/or dose of treatment with anti-TL1A therapies may vary according to the particular anti-cancer agent or combination thereof. An appropriate treatment time for a particular anti-TL1A therapeutic agent will be appreciated by the skilled artisan. The invention contemplates the continued assessment of optimal treatment schedules for each anti-TL1A therapeutic agent, where the TL1A-specific biomarker signature of the subject as determined by the methods of the invention is a factor in determining optimal treatment doses and schedules.

EXAMPLES

The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. One skilled in the art may develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the invention.

Example 1

Biomarker Signature for TL1A Signaling

$CD4^+$ T cells from normal individuals were treated with recombinant TL1A following priming with IL12 and IL18. RNA sequencing was utilized to measure TL1A mediated gene activation and to identify biomarkers responsive to TL1A signaling.

In one example, $CD4^+$ cells were isolated from normal donors, rested overnight, and then treated for 8 hours in three groups: untreated (UT), primed (IL12+IL18), and stimulated (IL12+IL18+TL1A)). RNA were isolated from the cells and used for Fluidigm qPCR for 24 genes (22 biomarker genes and 2 housekeeping ActB and EEF1A1). Real-time PCR of 22 genes validated these genes as markers for activation by TL1A (Figure 1). Genes used for validation are listed in Table 1.

Table 1: TL1A-specific Biomarker Signature

Gene Name	**Gene Name**	**Gene Name**
BIRC3	GBP1	RGS1
C17orf49	GBP4	SGK1
CCL20	GBP5	STAT1
CSF2	HAPLN3	TAP1
CD274	IRF1	TRAFD1
CD74	NFKBIA	IFNG

EPSTI1	NFKB2	
FAS	RELB	

Example 2

All primers were optimized for efficiency and absence of off-target amplification using cyber-green qPCR.

Table 2: Sequences of Primers and Probes

Transcript	**NCBI ID**	**Primer Sequence**	**Primer SEQ ID NO:**
IFNG	NM_000619.2	TTGGGTTCTCTTGGCTGTTACT	SEQ ID NO:1
		ATCCGCTACATCTGAATGACCTG	SEQ ID NO:2
RGS1	NM_002922.3	CTTGCCAACCAAACTGGTCAAA	SEQ ID NO:3
		ACAAGCCAGCCAGAACTCAATA	SEQ ID NO:4
GBP5	NM_001134486.1	GGTTGGCGGCGATTCAAAG	SEQ ID NO:5
		AGTCCTCTGGGCGTGCT	SEQ ID NO:6
GBP1	NM_002053.2	ACTTCAGGAACAGGAGCAACT	SEQ ID NO:7
		GGTACATGCCTTTCGTCGTCT	SEQ ID NO:8
IRF1	NM_002198.2	AGGAGGTGAAAGACCAGAGC	SEQ ID NO:9
		CTCTTAGCATCTCGGCTGGA	SEQ ID NO:10
STAT1	NM_007315	GTTTGACGAGGTGTCTCGGATAG	SEQ ID NO:11
		AACTGTCGCCAGAGAAGATGAA	SEQ ID NO:12
C17orf49	NM_001142798.1	TGCTCTGAACGACTCCGATG	SEQ ID NO:13
		AGAATCCAGGGTCAGGCTGT	SEQ ID NO:14
SGK1	NM_001143676.1	AGCAAGACACAAGGCAGAAGA	SEQ ID NO:15
		CAGAACATTCCGCTCCGACATA	SEQ ID NO:16
GBP4	NM_052941.4	GGACAGAGCAATGGGTGAGAG	SEQ ID NO:17
		ACTAGACAAATGGGGGCCATC	SEQ ID NO:18
EPSTI1	NM_001002264.1	GCAGCAGCAAGAGCAAGAAA	SEQ ID NO:19
		GGAGTCGGTCCAGAAAAGCA	SEQ ID NO:20
CD274	NM_014143.2	GTTGAAGGACCAGCTCTCCC	SEQ ID NO:21
		CTTGTAGTCGGCACCACCAT	SEQ ID NO:22
RELB	NM_006509.2	ATTGACCCCTACAACGCTGG	SEQ ID NO:23
		TCCGCAGCTCTGATGTGTTT	SEQ ID NO:24
NFKBIA	NM_020529.2	AAGTGATCCGCCAGGTGAAG	SEQ ID NO:25
		CTGCTCACAGGCAAGGTGTA	SEQ ID NO:26
NFKB2	NM_001077494.	CGCTTCTCTGCCTTCCTTAGAG	SEQ ID NO:27

	2		
		AGCCTGCTGTCTTGTCCATT	SEQ ID NO:28
CD74	NM_001025159.1	GCACTCCTTGGAGCAAAAGC	SEQ ID NO:29
		AAGACACACCAGCAGTAGCC	SEQ ID NO:30
TRAFD1	NM_001143906.1	GTGGTAGGAGTGAAGGTGGC	SEQ ID NO:31
		GCACAGAAGACAGGAACCGA	SEQ ID NO:32
TAP1	NM_000593.5	TTTGAGTACCTGGACCGCAC	SEQ ID NO:33
		AATGTCAGCCCCTGTAGCAC	SEQ ID NO:34
BIRC3	NM_182962	AGTGGTTTCCAAGGTGTGAGT	SEQ ID NO:35
		CTGGGCTGTCTGATGTGGATAG	SEQ ID NO:36
HAPLN3	NM_178232	CAACGGCTTCTACTACTCCAACA	SEQ ID NO:37
		CACCACCAGCTTCACTCCATTA	SEQ ID NO:38
FAS	NM_000043	ACTGTGACCCTTGCACCAAAT	SEQ ID NO:39
		GCCACCCCAAGTTAGATCTGG	SEQ ID NO:40
EEF1A1	NM_001402.5	CACACGGCTCACATTGCAT	SEQ ID NO:41
		CACGAACAGCAAAGCGACC	SEQ ID NO:42
ACTB	NM_001101.3	CGTGCTGCTGACCGAGG	SEQ ID NO:43
		AAGGTCTCAAACATGATCTGGGT	SEQ ID NO:44
CSF2	NM_000758.3	GAGACACTGCTGCTGAGATGAA	SEQ ID NO:45
		GGCTCCTGGAGGTCAAACAT	SEQ ID NO:46
CCL20	NM_004591.2	GTCTGTGTGCGCAAATCCAA	SEQ ID NO:47
		GAAACCTCCAACCCCAGCAA	SEQ ID NO:48
GADD45B-F		TGA ATG TGG ACC CAG ACA GC	SEQ ID NO:49
GADD45B-R		ACT GGA TGA GCG TGA AGT GG	SEQ ID NO:50
MFSD2A-F		GGA GCA GAG AGA ACC CTA TGA A	SEQ ID NO:51
MFSD2A-R		AGG TGA AGA GGA AGC CAG TAA	SEQ ID NO:52
TRAF4-F		CGT GAT CTA CCT GCA CAC TTG	SEQ ID NO:53
TRAF4-R		ACA TAC CCT CAT GGC TCT CAT A	SEQ ID NO:54
TNFRSF4-F		TGT AAC CTC AGA AGT GGG AGT G	SEQ ID NO:55
TNFRSF4-R		ACA GTC AAC TCC AGG CTT GT	SEQ ID NO:56
SLAMF7-sense		CCA ACA TGC CTC ACC CTC AT	SEQ ID NO:57
SLAMF7-Antisense		GGA ACC GAC CAG CTC TTT CA	SEQ ID NO:58
SLC7A5-F		CTC TTC CTG ATC GCC GTC TC	SEQ ID NO:59

SLC7A5-R		GAC CAC CTG CAT GAG CTT CT	SEQ ID NO:60
SOD2-F		CAC TGC AAG GAA CAA CAG GC	SEQ ID NO:61
SOD2-R		TGC TCC CAC ACA TCA ATC CC	SEQ ID NO:62
IRF4-F		GCC CAG CAG GTT CAC AAC TA	SEQ ID NO:63
IRF4-R		AGG TGG GGC ACA AGC ATA AA	SEQ ID NO:64
IL22-F		TGG GGA GAA ACT GTT CCA CG	SEQ ID NO:65
IL22-R		TGT GCT TAG CCT GTT GCT GA	SEQ ID NO:66
IL26-F		AAC GAT TCC AGA AGA CCG CA	SEQ ID NO:67
IL26-R		GAA AGT CCT CCA CAA AGC GT	SEQ ID NO:68
FEZ1-F		GCT CAC AGC AGA TCA GGT AAT TG	SEQ ID NO:69
FEZ1-R		TTT CTC CTC CAT CCT CTT CTT CC	SEQ ID NO:70
CHAC1-F		GCA GGG AGA CAC CTT CCA TC	SEQ ID NO:71
CHAC1-R		TCT TCA AGG AGC GTC ACC AC	SEQ ID NO:72
MYO1B-F		ACC GTG CTA ATG GGA AGA GTA	SEQ ID NO:73
MYO1B-R		CAC CAA TGG AAC CTC TGA CTT G	SEQ ID NO:74
HMSD-sense		CAA CGG GCT CTT TGG AGA AA	SEQ ID NO:75
HMSD-Antisense		CGT GTT GTG GAC TTC TCT GTA TC	SEQ ID NO:76
CD83-F		CGA AGA TGT GGA CTT GCC CT	SEQ ID NO:77
CD83-R		GGG GTG TCT CCA TCC TCT CT	SEQ ID NO:78
IL4I1-F		TCC GAG GAT GGC TTC TTC TAT C	SEQ ID NO:79
IL4I1-R		CGG CTG TAC TGG AGT CTG T	SEQ ID NO:80
DUSP5-F		GCT GAC ATT AGC TCC CAC TTT C	SEQ ID NO:81
DUSP5-R		GGA ACT GCT TGG TCT TCA TAA GG	SEQ ID NO:82
TNFRSF18-F		AGT GGG ACT GCA TGT GTG TC	SEQ ID NO:83
TNFRSF18-R		CAA GGT TTG CAG TGG CCT TC	SEQ ID NO:84
GADD45G-Sense		CTG CAT GAG TTG CTG CTG TC	SEQ ID NO:85
GADD45G-Antisense		GCA CTA TGT CGA TGT CGT TCT C	SEQ ID NO:86
BATF-F		GAA GAG TTC AGA GGA GGG AGA A	SEQ ID NO:87
BATF-R		GTA GAG CCG CGT TCT GTT TC	SEQ ID NO:88
LTA-F		TAC ACC TCC TCC TTC TGG GG	SEQ ID NO:89
LTA-R		TCC AAT GAG GTG AGC AGC AG	SEQ ID NO:90
CDKN1A-F		TGT GGA CCT GTC ACT GTC TT	SEQ ID NO:91
CDKN1A-R		GGC GTT TGG AGT GGT AGA AAT C	SEQ ID NO:92

IRF8-F		GGA CAT TTC CGA GCC ATA CAA A	SEQ ID NO:93
IRF8-R		ACC GCA CTC CAT CTC TGT AA	SEQ ID NO:94
PMAIP1-F		CGG AGA TGC CTG GGA AGA A	SEQ ID NO:95
PMAIP1-R		CTC CTG AGT TGA GTA GCA CAC T	SEQ ID NO:96
Furin F		AGC GGG ACC TGA ATG TGA AG	SEQ ID NO:97
Furin R		CGT GCC TGT TGT CAT TCA TCT	SEQ ID NO:98
TNF F		CCT GCT GCA CTT TGG AGT GA	SEQ ID NO:99
TNF R		ACA ACA TGG GCT ACA GGC TT	SEQ ID NO:100
HPRT1-F		CCC TGG CGT CGT GAT TAG TG	SEQ ID NO:101
HPRT1-R		TCG AGC AAG ACG TTC AGT CC	SEQ ID NO:102
SDHA-F		CTT GCC AGG ACC TAG AGT TTG T	SEQ ID NO:103
SDHA-R		CTC CAC GAC ATC CTT CCG TAA T	SEQ ID NO:104

Table 3: Information of Primers and Probes

Primer SEQ ID NO:	**Length**	**Start**	**Stop**	**Amplicon**	**Tm**	**GC%**	**Location**	**Primer final conc.**
SEQ ID NO:1	22	172	194	96	*56.3*	45	Exon1	125nM
SEQ ID NO:2	23	245	268		*56.6*	48	Exon2	
SEQ ID NO:3	22	334	356	87	*56.5*		Exon3/4	250nM
SEQ ID NO:4	22	399	421		*56.6*		Exon4	
SEQ ID NO:5	19	1938	1956	219	*57.4*	58	Exon 10	125nM
SEQ ID NO:6	17	2141	2157		59.2	65	Exon 11	
SEQ ID NO:7	21	1879	1899	112	56	47.62	Exon10	250nM
SEQ ID NO:8	21	1990	1970		57	52.38	Exon11	
SEQ ID NO:9	20	509	528	124	56.6	55	Exon4	125nM
SEQ ID NO:10	20	632	613		56.3	55	Exon5	
SEQ ID NO:11	23	2578	2601	99	*57*	52	Exon24	250nM
SEQ ID NO:12	22	2655	2677		*56.2*	45	Exon25	
SEQ ID NO:13	20	527	546	112	57	55	Exon5	250nM
SEQ ID NO:14	20	638	619		58.3	55	Exon6	
SEQ ID NO:15	21	1225	1246	109	56.9	48	Exon7	125nM
SEQ ID NO:16	22	1312	1334		56.7	50	Exon8	
SEQ ID NO:17	21	108	127	94	57.1	58	Exon1	250nM
SEQ ID NO:18	21	182	201		57	52.4	Exon2	
SEQ ID NO:19	20	904	923	80	56.6	50	Exon10	250nM
SEQ ID NO:20	20	964	983		57	55	Exon11	
SEQ ID NO:21	20	369	388	112	57.5	60	Exon3	250nM
SEQ ID NO:22	20	461	480		57.3	55	Exon4	
SEQ ID NO:23	20	870	889	175	*57.4*	55	Exon6/7	250nM
SEQ ID NO:24	20	1025	1044		*57*	55	Exon8	

SEQ ID NO:25	20	385	404	188	*57.4*	55	Exon2	250nM
SEQ ID NO:26	20	553	572		*57.3*	55	Exon3	
SEQ ID NO:27	22	844	865	139	57.1	54.5	Exon 8	250nM
SEQ ID NO:28	20	963	982		56.9	50	Exon 9	
SEQ ID NO:29	20	772	791	177	57.1	55	Exon7	250nM
SEQ ID NO:30	20	929	948		57.3	55	Exon9	
SEQ ID NO:31	20	2236	2255	173	57.6	60	Exon10/11	250nM
SEQ ID NO:32	20	2389	2408		57.2	55	Exon12	
SEQ ID NO:33	20	1770	1789	143	57.2	55	Exon7	250nM
SEQ ID NO:34	20	1893	1912		57.4	55	Exon7/8	
SEQ ID NO:35	21	1163	1184	117	56.4	48	Exon 4/5	250nM
SEQ ID NO:36	22	1258	1280		57	55	Exon 6	
SEQ ID NO:37	23	191	213	90	56.6	48	Exon2	250nM
SEQ ID NO:38	22	260	281		57	50	Exon3	
SEQ ID NO:39	21	770	791	105	57.3	47.6	Exon 4/5	250nM
SEQ ID NO:40	21	854	875		57.7	57.1	Exon 6	
SEQ ID NO:41	19	1153	1171	193	56.3	53	Exon7	62.5nM
SEQ ID NO:42	19	1327	1345		57.2	58	Exon7/8	
SEQ ID NO:43	17	390	406	75	59	71	Exon3	500nM
SEQ ID NO:44	23	442	464		56.3	44	Exon3/4	
SEQ ID NO:45	22	172	193	67	56.9	50	Exon 1	250nM
SEQ ID NO:46	20	219	238		57.2	55	Exon2/3	
SEQ ID NO:47	20			153				250nM
SEQ ID NO:48	20							

Example 3

Methods and Materials

A. RNA Sequencing and Analysis

Samples were prepared with the Illumina TruSeq RNA library preparation kit and sequenced on the Illumina GA IIx.

RNA sequencing data were prescreened: all failed probe data were removed and all genes with fewer than 3 samples (out of 12) with FPKM>5 were removed. Total 8695 genes passed prescreen (out of 24789).

RNA sequencing data were analyzed using BRB Array Tools developed by Richard Simon & BRB-ArrayTools Development Team. It is available at the website of Biometric

Research Branch, Division of Cancer Treatment and Diagnosis, National Cancer Institute. BRB-ArrayTools is an integrated package for the visualization and statistical analysis of DNA microarray gene expression data. It was developed by professional statisticians experienced in the analysis of microarray data and involved in the development of improved methods for the design and analysis of microarray based experiments. The array tools package utilizes an Excel front end. Scientists are familiar with Excel and utilizing Excel as the front end makes the system portable and not tied to any database. The input data is assumed to be in the form of Excel spreadsheets describing the expression values and a spreadsheet providing user-specified phenotypes for the samples arrayed. The analytic and visualization tools are integrated into Excel as an add-in. The analytic and visualization tools themselves are developed in the powerful R statistical system, in C and Fortran programs and in Java applications. Visual Basic for Applications is the glue that integrates the components and hides the complexity of the analytic methods from the user. The system incorporates a variety of powerful analytic and visualization tools developed specifically for microarray data analysis. In one example, genes with highest 20% variance were selected and genes missing >50% values were eliminated.

B. Real-time PCR

Fluidigm qPCR technology was used. In one example, PCR was performed in 48x48 format according to protocol with modification of primer concentrations which were adjusted to optimal concentrations as noted in Table 3.

C. Cell Isolation and Culture

PBMC (peripheral blood mononuclear cells) were isolated from healthy volunteers by separation on Ficoll-Hypaque gradients. CD4$^+$ T cells were isolated according to manufacturer's recommendations using negative selection by depletion with magnetic beads (Stemcell Technologies, Vancouver, BC, Canada) and were at least 95% pure.

CD4$^+$ T cells were cultured overnight (37°C with 5% CO2) in RPMI 1640 with 10% fetal calf serum. For the primed group (IL12+IL18), cells were treated with IL-12 (0.5 ng/ml) and IL-18 (50 ng/ml) for 8 hours at 37°C prior to RNA isolation. For the TL1A-stimulated group (IL12+IL18+TL1A), cells were treated with IL-12 (0.5 ng/ml), IL-18 (50 ng/ml), and recombinant TL1A (100 ng/ml) (Fitzgerald, North Acton, MA) for 8 hours at 37°C prior to RNA isolation. RNA was isolated using RNeasy Plus Mini Kit (Qiagen, Germantown, MD). Other examples are described in Papadakis et al. (TL1A synergizes with IL-12 and IL-18 to enhance IFN-gamma production in human T cells and NK cells; J Immunol. 2004 Jun 1;172(11):7002-7), which is incorporated herein by reference as though fully set forth.

Other examples are described in Papadakis et al. (TL1A synergizes with IL-12 and IL-18 to enhance IFN-gamma production in human T cells and NK cells; J Immunol. 2004 Jun 1;172(11):7002-7), which is incorporated herein by reference as though fully set forth.

Example 4

Table 4: Top TL1A Response Genes from IFN-γ-Secreting Cells

Gene	**p-value**	**FDR**
BATF	< 1e-07	< 1e-07
CCL20	2.00E-07	1.33E-06
CD274	< 1e-07	< 1e-07
CD83	< 1e-07	< 1e-07
CDKN1A	3.20E-06	1.17E-05
CHAC1	< 1e-07	< 1e-07
CSF2	9.00E-07	4.30E-06
DUSP5	< 1e-07	< 1e-07
FEZ1	4.00E-07	2.28E-06
GADD45G	1.00E-07	7.67E-07
HMSD	3.63E-04	6.50E-04
IFNG	< 1e-07	< 1e-07
IL22	< 1e-07	< 1e-07
IL26	2.00E-07	1.33E-06
IL4I1	1.20E-05	3.45E-05
IRF8	3.02E-05	7.42E-05
LTA	< 1e-07	< 1e-07
MFSD2A	1.23E-05	3.52E-05
MYO1B	< 1e-07	< 1e-07
NFKBIA	< 1e-07	< 1e-07
RPL21	< 1e-07	< 1e-07

SGK1	< 1e-07	< 1e-07
TNFRSF18	9.00E-07	4.30E-06
TNFRSF4	4.64E-05	1.07E-04
TRAF4	< 1e-07	< 1e-07
XIST	1.30E-04	2.62E-04

Example 5

In one example, 20 normal control (NL), 20 CD, and 18 UC samples were rested overnight, activated for 8 hours with (IL12+IL18) or (IL12+IL18/TL1A) , and analyzed for expression levels of 48 genes. In another example, 21 NL, 15 NL-H, 20 CD, and 18 UC samples were rested overnight, activated for 8 hours with (IL12+IL18) or (IL12+IL18+TL1A) , and analyzed for expression levels of 20 genes. Results are shown in Figures 7-13 and Table 5.

Table 5: Expression Levels Differ in IBD vs. NL (p values)

GENE	**UT**	**12+18**	**TL1A**
C17orf49		Upregulated (0.0149)	
CCL20		Downregulated (0.0479)	Downregulated (0.0015)
CD274		Upregulated (0.0228)	
CD83		Upregulated (0.004)	
CDKN1A		Upregulated (0.0296)	
CHAC1		Upregulated (0.0033)	
CSF2			Downregulated (0.0219)
DUSP5		Upregulated (0.027)	
EPSTI1			Downregulated (0.0036)
FAS		Downregulated (0.0049)	Downregulated (0.0004)
FURIN		Upregulated (0.0473)	
GADD45G		Upregulated (0.0397)	
GBP1		Upregulated (0.0359)	Downregulated (0.0234)
GBP4			Downregulated (0.0322)
GBP5			Downregulated (0.0049)
HAPLN3	Downregulated (0.0004)	Downregulated (0.0002)	Downregulated (0.0001)
HMSD		Upregulated (0.0236)	
IFNG			Downregulated (0.0419)
IL22		Upregulated (0.0115)	

IL26		Upregulated (0.0197)	
IL4I1	Upregulated (0.0126)	Upregulated (0.003)	
IRF1		Upregulated (0.0229)	
LTA		Upregulated (0.0119)	
MFSD2A			Downregulated (0.044)
MYO1B		Upregulated (0.0218)	
NFKB1A			Downregulated (0.0434)
NFKB2			Downregulated (0.0097)
PMAIP1	Upregulated (0.0045)	Upregulated (0.0016)	
RGS1			Downregulated (0.0066)
SGK1	Upregulated (0.0001)	Upregulated (0.0002)	
SLAMF7	Upregulated (0.0342)	Upregulated (0.0023)	
SOD2		Upregulated (0.0163)	
STAT1			Downregulated (0.0029)
TAP1			Downregulated (0.0297)
TNF			Downregulated (0.0428)
TNFRSF18		Upregulated (0.0283)	
TNFRSF4			Downregulated (0.018)
TRAF4			Downregulated (0.0013)
TRAFD1		Upregulated (0.0097)	

Example 6

Table 6: List of Genes

ACTB	DUSP5	HAPLN3	MFSD2A	SLAMF7
BATF	EEF1A1	HMSD	MYO1B	SLC7A5
BIRC3	EPSTI1	HPRT1	NFKB1A	SOD2
C17orf49	FAS	IFNG	NFKB2	STAT1
CCL20	FEZ1	IL22	NFKBIA	TAP1
CD274	Furin	IL26	PMAIP1	TNF
CD74	GADD45B	IL4I1	RELB	TNFRSF18
CD83	GADD45G	IRF1	RGS1	TNFRSF4
CDKN1A	GBP1	IRF4	RPL21	TRAF4
CHAC1	GBP4	IRF8	SDHA	TRAFD1

CSF2	GBP5	LTA	SGK1	XIST

The various methods and techniques described above provide a number of ways to carry out the application. Of course, it is to be understood that not necessarily all objectives or advantages described can be achieved in accordance with any particular embodiment described herein. Thus, for example, those skilled in the art will recognize that the methods can be performed in a manner that achieves or optimizes one advantage or group of advantages as taught herein without necessarily achieving other objectives or advantages as taught or suggested herein. A variety of alternatives are mentioned herein. It is to be understood that some preferred embodiments specifically include one, another, or several features, while others specifically exclude one, another, or several features, while still others mitigate a particular feature by inclusion of one, another, or several advantageous features.

Furthermore, the skilled artisan will recognize the applicability of various features from different embodiments. Similarly, the various elements, features and steps discussed above, as well as other known equivalents for each such element, feature or step, can be employed in various combinations by one of ordinary skill in this art to perform methods in accordance with the principles described herein. Among the various elements, features, and steps some will be specifically included and others specifically excluded in diverse embodiments.

Although the application has been disclosed in the context of certain embodiments and examples, it will be understood by those skilled in the art that the embodiments of the application extend beyond the specifically disclosed embodiments to other alternative embodiments and/or uses and modifications and equivalents thereof.

In some embodiments, the terms “a” and “an” and “the” and similar references used in the context of describing a particular embodiment of the application (especially in the context of certain of the following claims) can be construed to cover both the singular and the plural. The recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (for example, “such as”) provided with respect to certain embodiments herein is intended merely to better illuminate the application and does not pose a limitation on the scope of the application otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the application.

Preferred embodiments of this application are described herein, including the best mode known to the inventors for carrying out the application. Variations on those preferred embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. It is contemplated that skilled artisans can employ such variations as appropriate, and the application can be practiced otherwise than specifically described herein. Accordingly, many embodiments of this application include all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the application unless otherwise indicated herein or otherwise clearly contradicted by context.

All patents, patent applications, publications of patent applications, and other material, such as articles, books, specifications, publications, documents, things, and/or the like, referenced herein are hereby incorporated herein by this reference in their entirety for all purposes, excepting any prosecution file history associated with same, any of same that is inconsistent with or in conflict with the present document, or any of same that may have a limiting affect as to the broadest scope of the claims now or later associated with the present document. By way of example, should there be any inconsistency or conflict between the description, definition, and/or the use of a term associated with any of the incorporated material and that associated with the present document, the description, definition, and/or the use of the term in the present document shall prevail.

It is to be understood that the embodiments of the application disclosed herein are illustrative of the principles of the embodiments of the application. Other modifications that can be employed can be within the scope of the application. Thus, by way of example, but not of limitation, alternative configurations of the embodiments of the application can be utilized in accordance with the teachings herein. Accordingly, embodiments of the present application are not limited to that precisely as shown and described.

Various embodiments of the invention are described above in the Detailed Description.

While these descriptions directly describe the above embodiments, it is understood that those skilled in the art may conceive modifications and/or variations to the specific embodiments shown and described herein. Any such modifications or variations that fall within the purview of this description are intended to be included therein as well. Unless specifically noted, it is the intention of the inventors that the words and phrases in the specification and claims be given the ordinary and accustomed meanings to those of ordinary skill in the applicable art(s).

The foregoing description of various embodiments of the invention known to the applicant at this time of filing the application has been presented and is intended for the purposes of illustration and description. The present description is not intended to be exhaustive nor limit the invention to the precise form disclosed and many modifications and variations are possible in the light of the above teachings. The embodiments described serve to explain the principles of the invention and its practical application and to enable others skilled in the art to utilize the invention in various embodiments and with various modifications as are suited to the particular use contemplated. Therefore, it is intended that the invention not be limited to the particular embodiments disclosed for carrying out the invention.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that, based upon the teachings herein, changes and modifications may be made without departing from this invention and its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as are within the true spirit and scope of this invention. It will be understood by those within the art that, in general, terms used herein are generally intended as “open” terms (*e.g.*, the term “including” should be interpreted as “including but not limited to,” the term “having” should be interpreted as “having at least,” the term “includes” should be interpreted as “includes but is not limited to,” etc.)

WHAT IS CLAIMED IS:

1. A method of selecting a treatment for a subject, comprising:

    obtaining a sample from the subject;

    assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample;

    comparing the expression level to a reference value of expression level of the one or more biomarkers associated with TL1A signaling; and

    prescribing an anti-TL1A therapy to the subject if the subject has a high expression level relative to the reference value of one or more biomarkers associated with TL1A signaling, or prescribing no anti-TL1A therapy to the subject if the subject does not have a high expression level relative to the reference value of one or more biomarkers associated with TL1A signaling.
2. The method of claim 1, further comprising stimulating the sample with IL12, IL18, or TL1A, or a combination thereof, before assaying the expression level of one or more biomarkers associated with TL1A signaling in the sample.
3. The method of claim 1, wherein the one or more biomarkers associated with TL1A signaling is listed in Table 1, Table 4, Table 5 and/or Table 6 herein.
4. The method of claim 1, wherein the one or more biomarkers associated with TL1A signaling is selected from the group consisting of BIRC3, C17orf49, CCL20, CSF2, CD274, CD74, EPSTI1, FAS, GBP1, GBP4, GBP5, HAPLN3, IFNG, IRF1, NFKBIA, NFKB2, RELB, RGS1, SGK1, STAT1, TAP1, and TRAFD1.
5. The method of claim 1, wherein the one or more biomarkers associated with TL1A signaling is selected from the group consisting of BATF, CCL20, CD274, CD83, CDKN1A, CHAC1, CSF2, DUSP5, FEZ1, GADD45G, HMSD, IFNG, IL22, IL26, IL4I1, IRF8, LTA, MFSD2A, MYO1B, NFKBIA, RPL21, SGK1, TNFRSF18, TNFRSF4, TRAF4, and XIST.
6. The process of claim 1, wherein the subject is human.
7. The method of claim 1, wherein the subject has a symptom of a TL1A-associated disease.
8. The method of claim 1, wherein the subject is suspected of having a TL1A-associated disease.

9. The method of claim 1, wherein the subject is diagnosed with a TL1A-associated disease.

10. The method of claim 1, wherein the sample comprises a T cell, CD4$^+$ T cell, CD8$^+$ T cell, CD56$^+$ T cell, CD45R0$^+$ T cell, CD45RA$^+$ T cell, NK cell, peripheral blood mononuclear cell (PBMC), or peripheral blood lymphocyte (PBL), or a combination thereof.

11. The method of claim 7, wherein the TL1A associated disease is fibrosis, Crohn's disease (CD), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease, allergic lung inflammation, asthma, atherosclerosis, lupus, rheumatoid arthritis (RA), multiple sclerosis (MS), psoriasis, type 1 diabetes, lung carcinoma, colon carcinoma, leukemia, lymphoma, transplant rejection, graft versus host disease, or central nervous system injury.

12. The method of claim 2, wherein assaying the expression level of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6 in the sample comprises assaying an mRNA level.

13. The method of claim 12, wherein assaying an mRNA level comprises using RNA sequencing, northern blot, *in situ* hybridization, hybridization array, serial analysis of gene expression (SAGE), reverse transcription PCR, real-time PCR, real-time reverse transcription PCR, or quantitative PCR, or a combination thereof.

14. The process of claim 12, wherein assaying an mRNA level comprises contacting the sample with a polynucleotide probe capable of specifically hybridizing to mRNA of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6 and thereby forming a probe-target hybridization complex.

15. The process of claim 12, wherein assaying an mRNA level comprises contacting the sample with one or more polynucleotide primers capable of specifically hybridizing to mRNAs of genes listed in Table 1, Table 4, Table 5 and/or Table 6, forming a primer-template hybridization complex, and performing a PCR reaction.

16. The process of claim 15, wherein the one or more polynucleotide primers are primers listed in Table 2.

17. The method of claim 1, wherein assaying the expression level of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6 in the sample comprises assaying a protein level.

18. The method of claim 17, wherein assaying a protein level comprises using western blot, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, or mass spectrometry, or a combination thereof.

19. The method of claim 17, wherein assaying a protein level comprises contacting the sample with antibodies capable of specifically binding to proteins of genes listed in Table 1, Table 4, Table 5 and/or Table 6 and thereby forming antigen-antibody complexes.

20. The method of claim 1, wherein the reference value of expression level is the median or mean expression level from a population of subjects who have no TL1A-associated disease.

21. The method of claim 1, wherein the reference value of expression level is the median or mean expression level from a population of subjects who are unlikely to be responsive to an anti-TL1A therapy.

22. The method of claim 1, wherein the reference value of expression level is the median or mean expression level from a population of subjects who are not responsive to an anti-TL1A therapy.

23. The method of claim 1, wherein the anti-TL1A therapy comprises an anti-TL1A antibody or a fragment thereof.

24. The method of claim 1, wherein the anti-TL1A therapy comprises an anti-DR3 antibody or a fragment thereof.

25. The method of claim 1, wherein the anti-TL1A therapy comprises a soluble decoy DR3 polypeptide, a polypeptide comprising a DR3 extracellular domain, or a polypeptide comprising a DR3 pre-ligand assembly domain, or a combination thereof.

26. The method of claim 1, wherein the anti-TL1A therapy comprises a nucleic acid antagonist of TL1A, or a nucleic acid antagonist of DR3, or a combination thereof.

27. The method of claim 1, wherein the anti-TL1A therapy comprises a GEP peptide, Atsttrin or a variant thereof, or a combination thereof.

28. The method of claim 2, wherein assaying the expression levels of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6 in the sample comprises assaying the expression levels of at least two genes listed in Table 1, Table 4, Table 5 and/or Table 6.

29. The method of claim 2, wherein assaying the expression levels of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6 in the sample comprises assaying the expression levels of at least three genes listed in Table 1, Table 4, Table 5 and/or Table 6.

30. The method of claim 2, wherein assaying the expression levels of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6 in the sample comprises assaying the expression levels of at least four genes listed in Table 1, Table 4, Table 5 and/or Table 6.

31. The method of claim 2, wherein assaying the expression levels of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6 in the sample comprises assaying the expression levels of at least five genes listed in Table 1, Table 4, Table 5 and/or Table 6.

32. The method of claim 2, wherein assaying the expression levels of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6 in the sample comprises assaying the expression levels of all genes listed in Table 1, Table 4, Table 5 and/or Table 6.

33. A method of treating a subject, comprising:

obtaining a sample from the subject;

assaying the expression level of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6 in the sample;

comparing the expression level to a reference value of expression level of the one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6; and

administering an anti-TL1A therapy to the subject if the subject has a high expression level relative to the reference value of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6, or administering no anti-TL1A therapy to the subject if the subject does not have a high expression level relative to the reference value of any of the genes listed in Table 1, Table 4, Table 5 and/or Table 6.

34. The method of claim 33, wherein the one or more genes is selected from the group consisting of BIRC3, C17orf49, CCL20, CSF2, CD274, CD74, EPSTI1, FAS, GBP1, GBP4, GBP5, HAPLN3, IFNG, IRF1, NFKBIA, NFKB2, RELB, RGS1, SGK1, STAT1, TAP1, and TRAFD1.

35. The method of claim 33, wherein the one or more genes is selected from the group consisting of BATF, CCL20, CD274, CD83, CDKN1A, CHAC1, CSF2, DUSP5, FEZ1, GADD45G, HMSD, IFNG, IL22, IL26, IL4I1, IRF8, LTA, MFSD2A, MYO1B, NFKBIA, RPL21, SGK1, TNFRSF18, TNFRSF4, TRAF4, and XIST.

36. A method, comprising:

obtaining a sample from a subject;

assaying the expression level of one or more genes listed in Table 1, Table 4, Table 5 and/or Table 6 herein in the sample;

comparing the expression level to a reference value of expression level of the one or more genes; and

diagnosing a disease in the subject according to the relative difference between the expression level and the reference value.

37. The method of claim 36, further comprising stimulating the sample with IL12, IL18, or TL1A, or a combination thereof, before assaying the expression level of one or more genes in the sample.

38. The method of claim 36, further comprising diagnosing the disease in the subject if the subject has an expression level higher than the reference value, or not diagnosing the disease in the subject if the subject does not have an expression level higher than the reference value.

39. The method of claim 36, further comprising diagnosing the disease in the subject if the subject has an expression level lower than the reference value, or not diagnosing the disease subtype in the subject if the subject does not have an expression level lower than the reference value.

40. The method of claim 36, wherein the disease is a TL1A-associated disease.

41. The method of claim 36, wherein the disease is fibrosis, Crohn's disease (CD), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease, allergic lung inflammation, asthma, atherosclerosis, lupus, rheumatoid arthritis (RA), multiple sclerosis (MS), psoriasis, type 1 diabetes, lung carcinoma, colon carcinoma, leukemia, lymphoma, transplant rejection, graft versus host disease, or central nervous system injury.

42. The method of claim 36, wherein the disease is an IBD subtype responsive to an anti-TL1A therapy.

43. The method of claim 36, wherein the subject is a human.

44. The method of claim 36, wherein the subject has a symptom of an IBD subtype.

45. The method of claim 36, wherein the subject is suspected of having an IBD subtype.

46. The method of claim 36, wherein the one or more genes is selected from the group consisting of BIRC3, C17orf49, CCL20, CSF2, CD274, CD74, EPSTI1, FAS, GBP1, GBP4, GBP5, HAPLN3, IFNG, IRF1, NFKBIA, NFKB2, RELB, RGS1, SGK1, STAT1, TAP1, and TRAFD1.

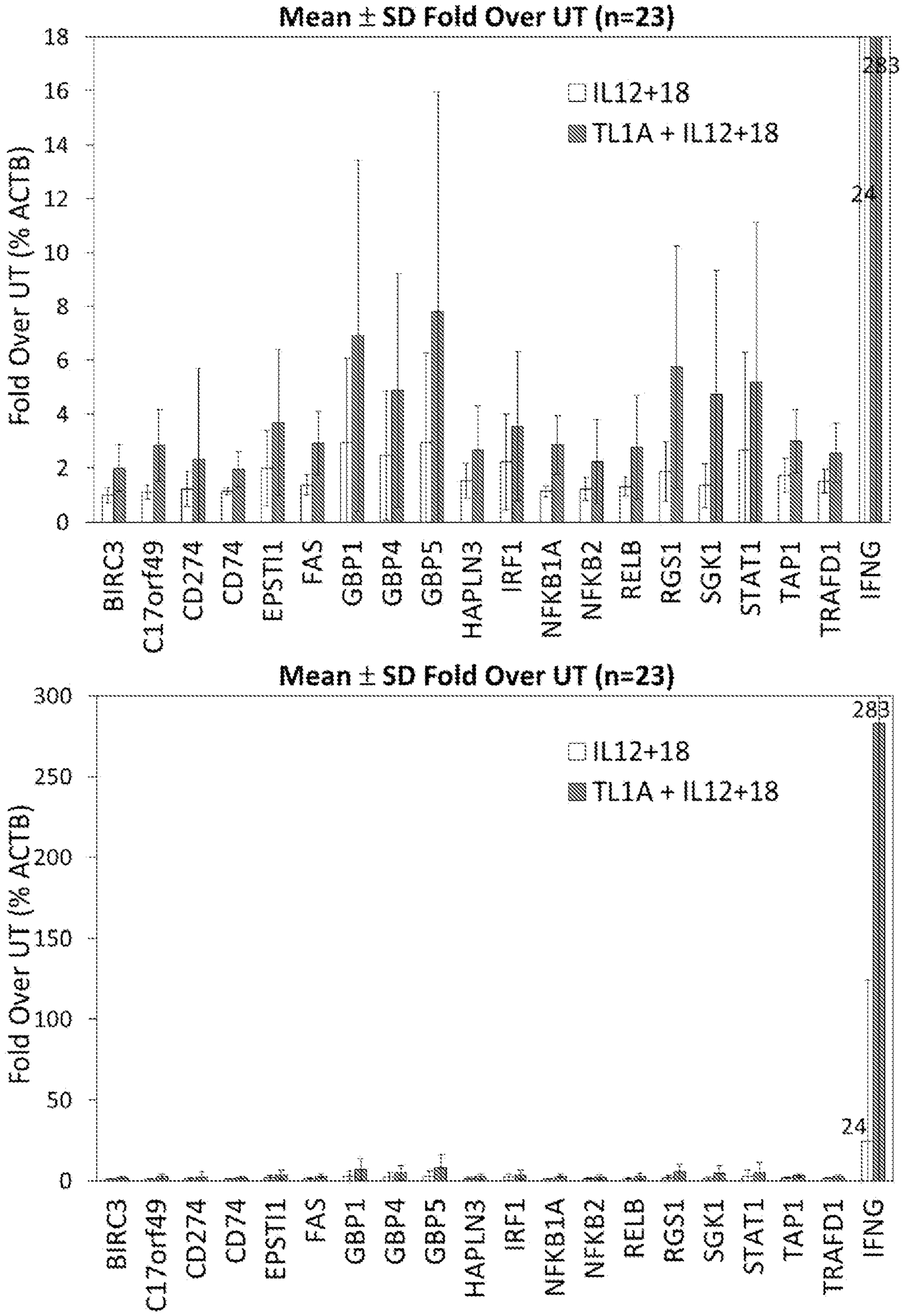
47. The method of claim 36, wherein the one or more genes is selected from the group consisting of BATF, CCL20, CD274, CD83, CDKN1A, CHAC1, CSF2, DUSP5, FEZ1, GADD45G, HMSD, IFNG, IL22, IL26, IL4I1, IRF8, LTA, MFSD2A, MYO1B, NFKBIA, RPL21, SGK1, TNFRSF18, TNFRSF4, TRAF4, and XIST.

48. The method of claim 36, wherein the sample comprises a T cell, $CD4^+$ T cell, $CD8^+$ T cell, $CD56^+$ T cell, $CD45R0^+$ T cell, $CD45RA^+$ T cell, NK cell, peripheral blood mononuclear cell (PBMC), or peripheral blood lymphocyte (PBL), or a combination thereof.

49. The method of claim 36, further comprising prescribing an anti-TL1A therapy to the subject if the subject is diagnosed with the disease.

50. The method of claim 36, further comprising administering an anti-TL1A therapy to the subject if the subject is diagnosed with the disease.

Figure 1



Mean ± SD Fold Over UT (n=23)

Mean ± SD Fold Over UT (n=23)

Figure 2

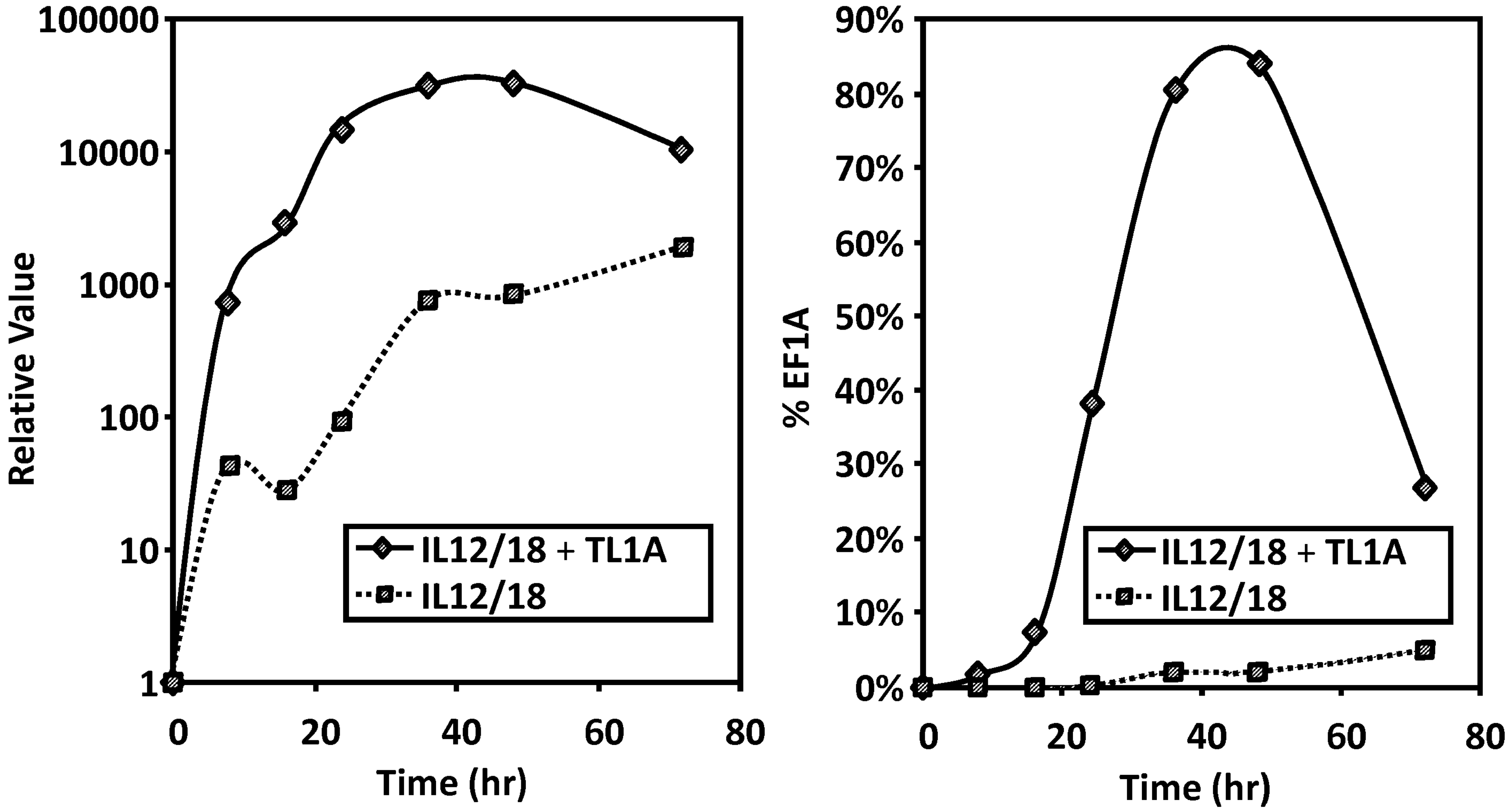
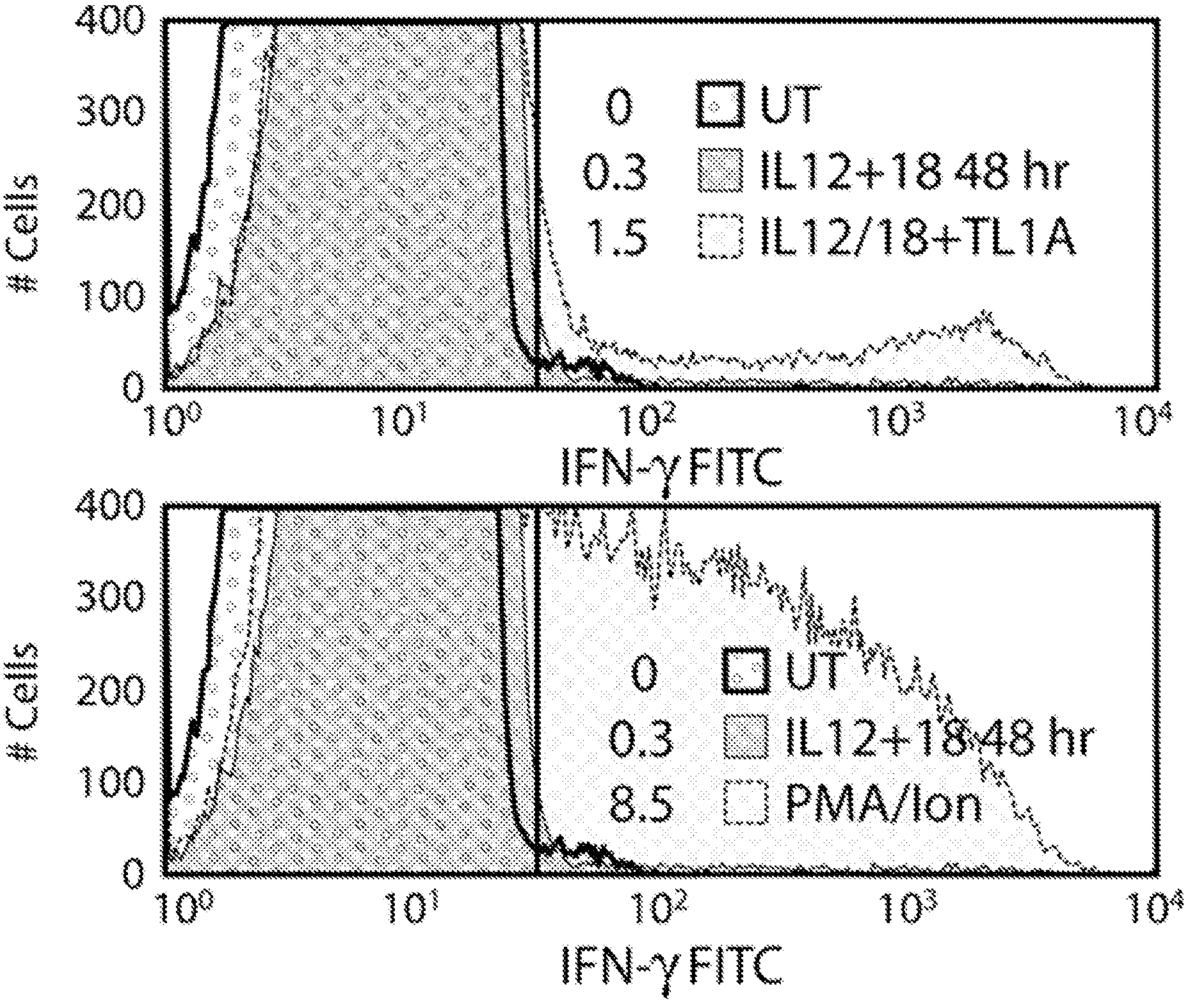

100000
10000
1000
100
10
1
Relative Value
0
20
40
60
80
Time (hr)
IL12/18 + TL1A
IL12/18
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
% EF1A
0
20
40
60
80
Time (hr)
IL12/18 + TL1A
IL12/18

Figure 3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300
200
100
0
Cells
10⁰
10¹
10²
10³
10⁴
IFN-γ FITC
0 UT
0.3 IL12+18 48 hr
1.5 IL12/18+TL1A
400
300
200
100
0
Cells
10⁰
10¹
10²
10³
10⁴
IFN-γ FITC
0 UT
0.3 IL12+18 48 hr
8.5 PMA/Ion

Figure 4

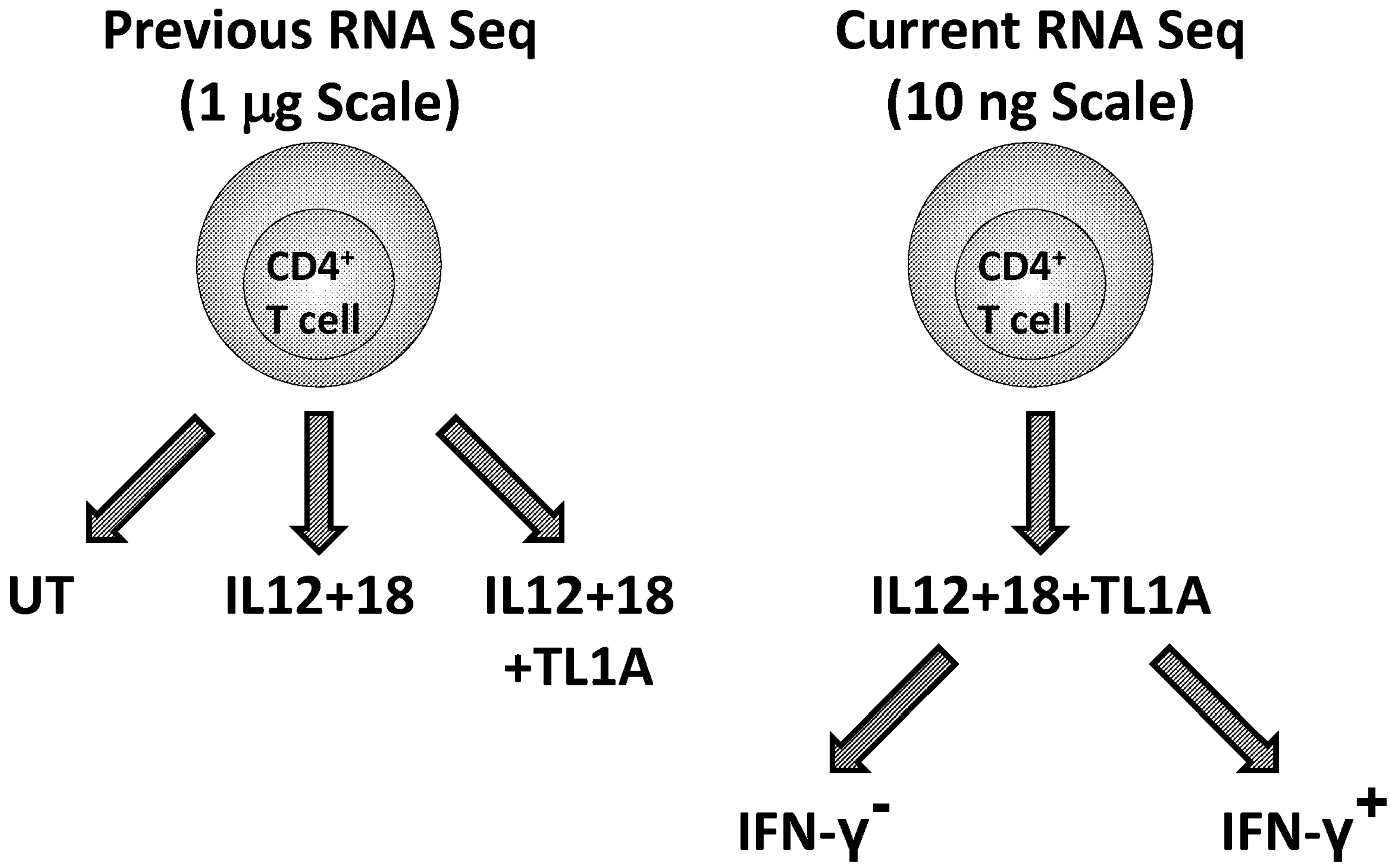

Previous RNA Seq
(1 µg Scale)
CD4+
T cell
UT
IL12+18
IL12+18
+TL1A
Current RNA Seq
(10 ng Scale)
CD4+
T cell
IL12+18+TL1A
IFN-γ-
IFN-γ+

Figure 5

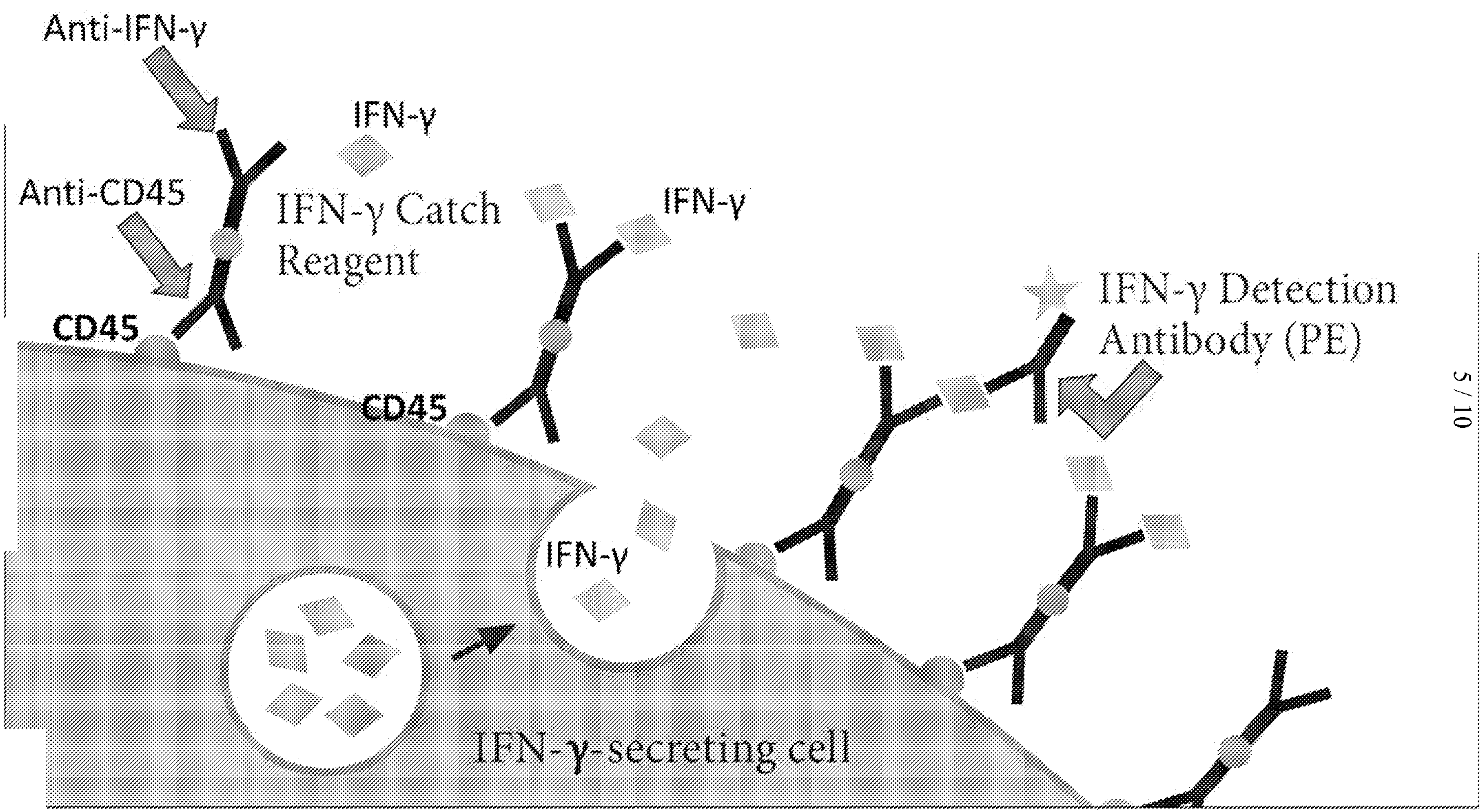
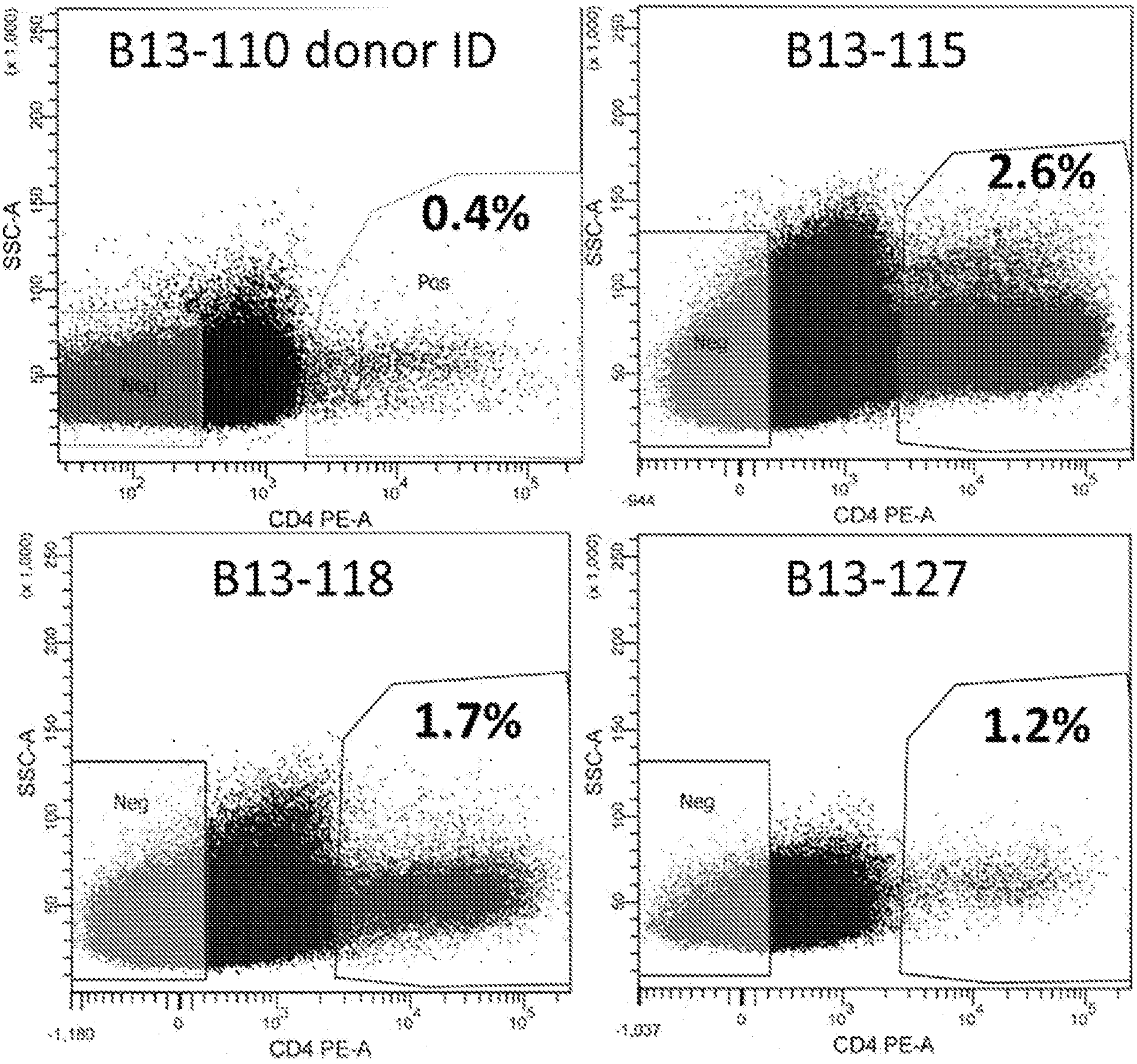

Anti-IFN-γ
IFN-γ
Anti-CD45
IFN-γ Catch
Reagent
CD45
IFN-γ
CD45
IFN-γ Detection
Antibody (PE)
IFN-γ
IFN-γ-secreting cell

Figure 6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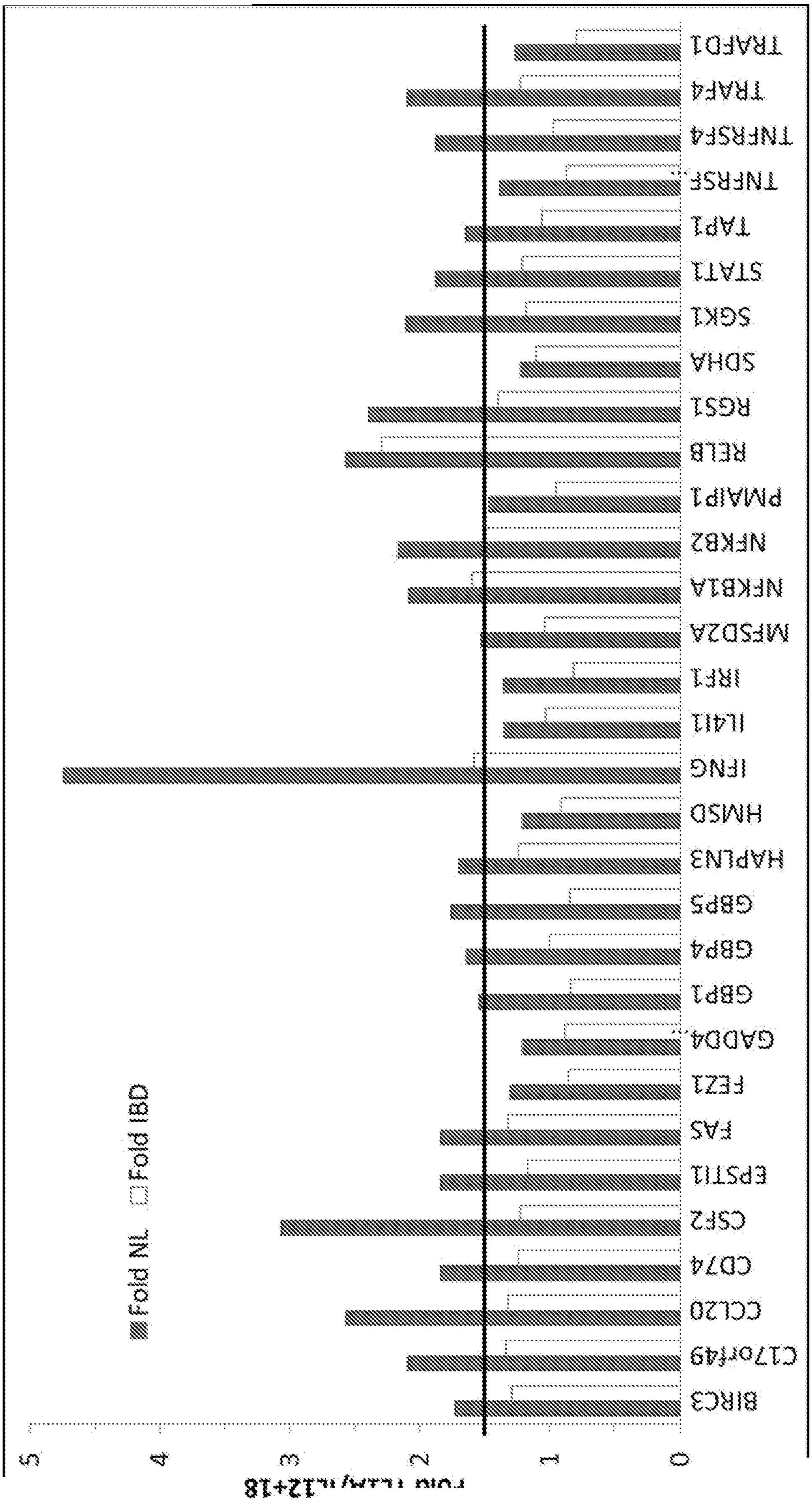
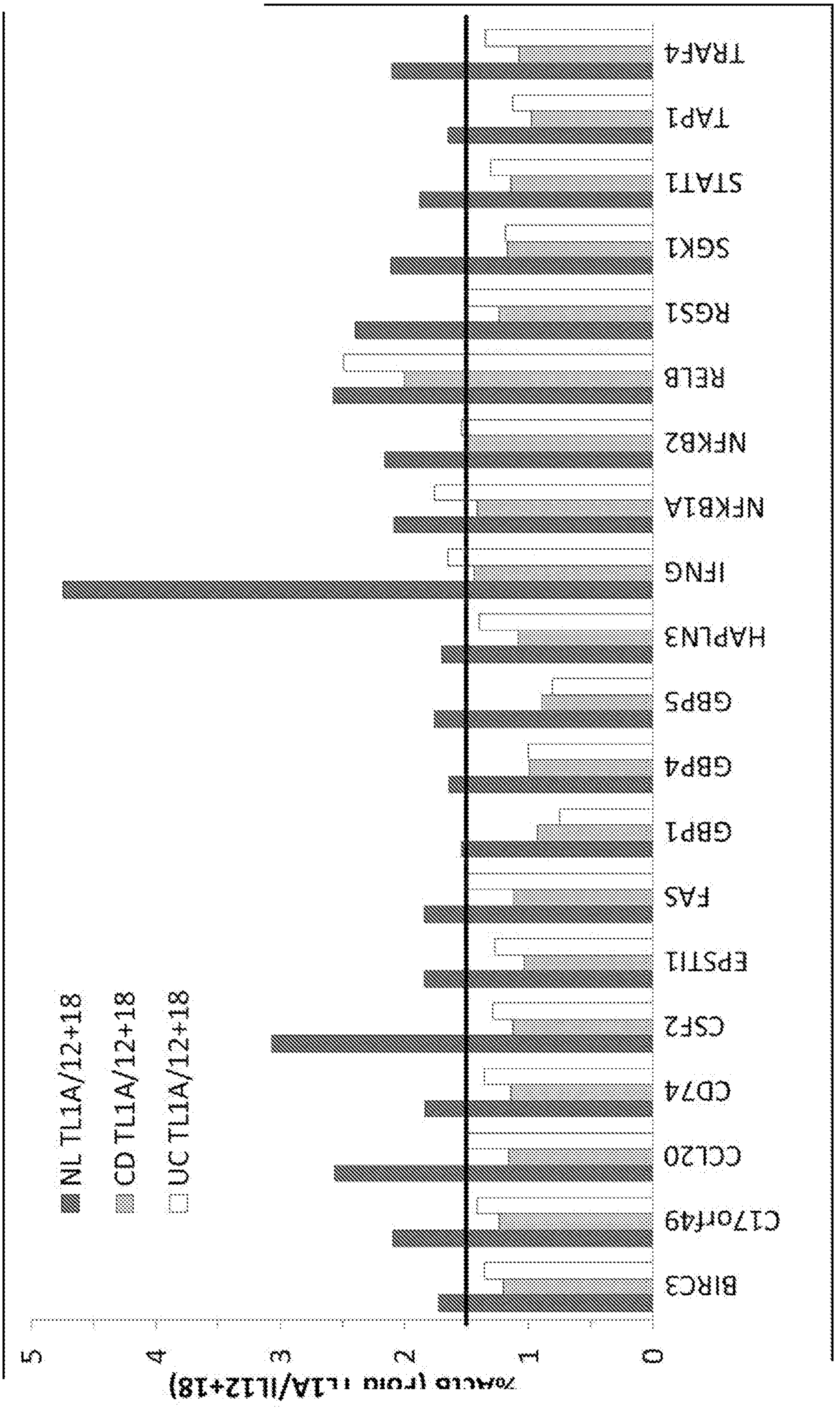
Pos
Neg
SSC-A
(x 1,000)
50
100
150
200
250
CD4 PE-A
10^2
10^3
10^4
10^5
B13-115
2.6%
Neg
-944
0
B13-118
1.7%
Neg
-1,180
B13-127
1.2%
Neg
-1,037

Figure 7


Fold NL
Fold IBD
TRAFD1
TRAF4
TNFRSF4
TNFRSF...
TAP1
STAT1
SGK1
SDHA
RGS1
RELB
PMAIP1
NFKB2
NFKB1A
MFSD2A
IRF1
IL4I1
IFNG
HMSD
HAPLN3
GBP5
GBP4
GBP1
GADD4...
FEZ1
FAS
EPSTI1
CSF2
CD74
CCL20
C17orf49
BIRC3
5
4
3
2
1
0
12+18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CD TL1A/12+18
UC TL1A/12+18
%ACTB (from TL1A/IL12+18)
0
1
2
3
4
5
BIRC3
C17orf49
CCL20
CD74
CSF2
EPSTI1
FAS
GBP1
GBP4
GBP5
HAPLN3
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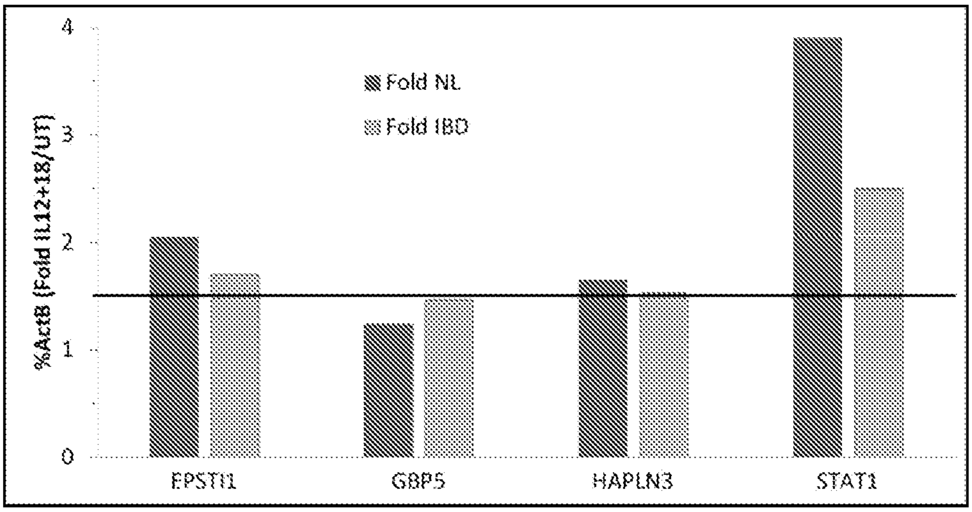
NFKB2
RELB
RGS1
SGK1
STAT1
TAP1
TRAF4

Figure 8

Figure 9



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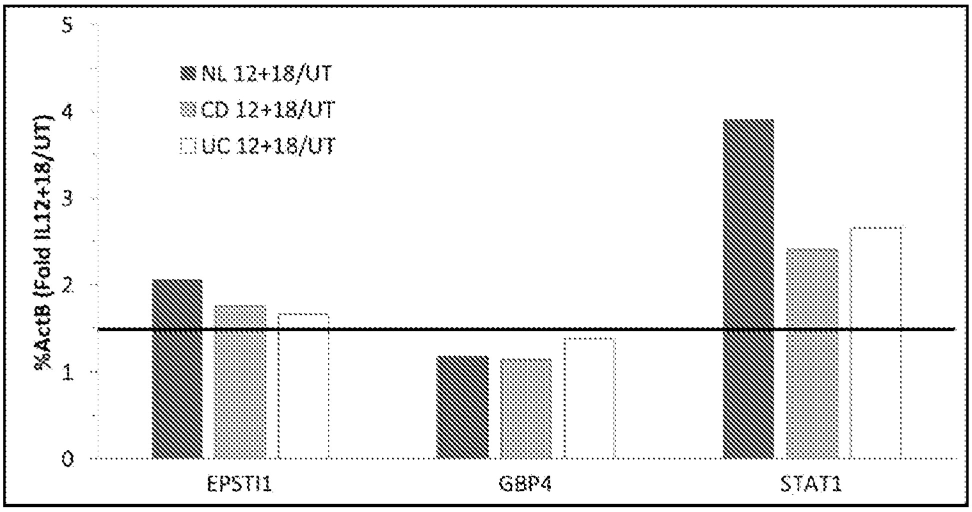

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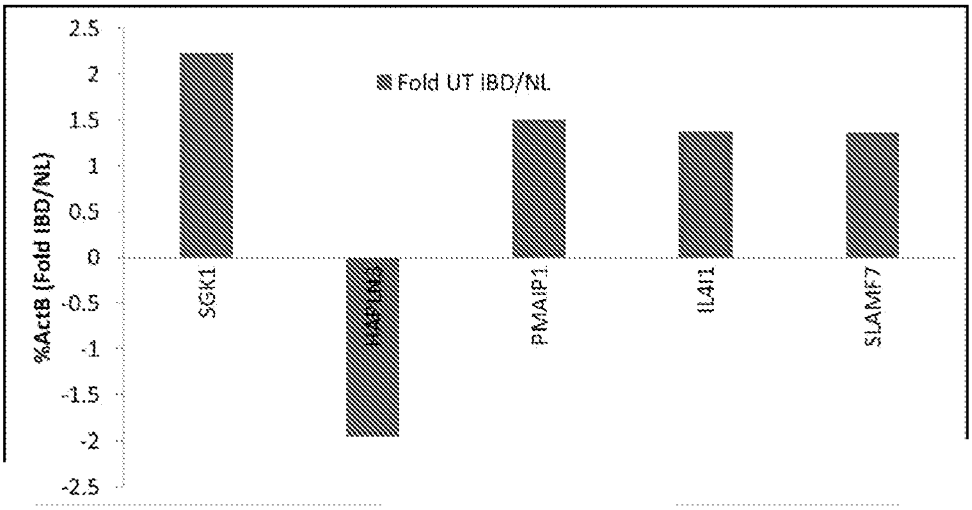

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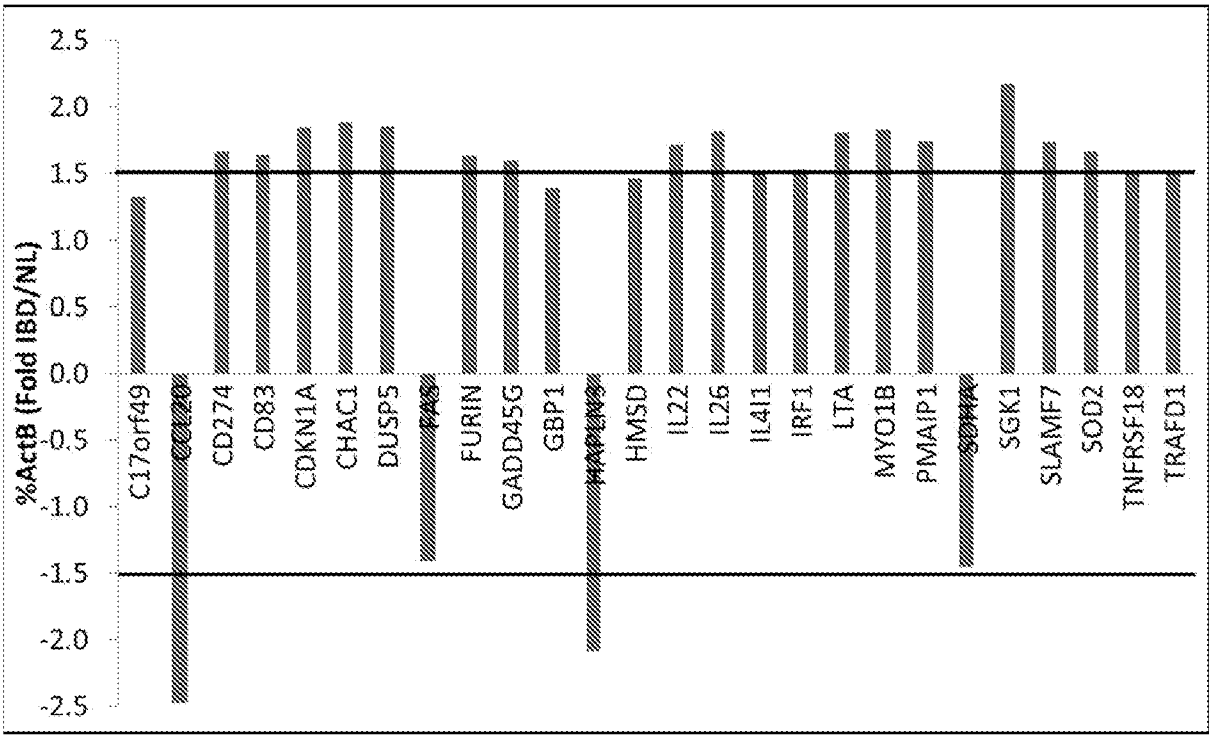

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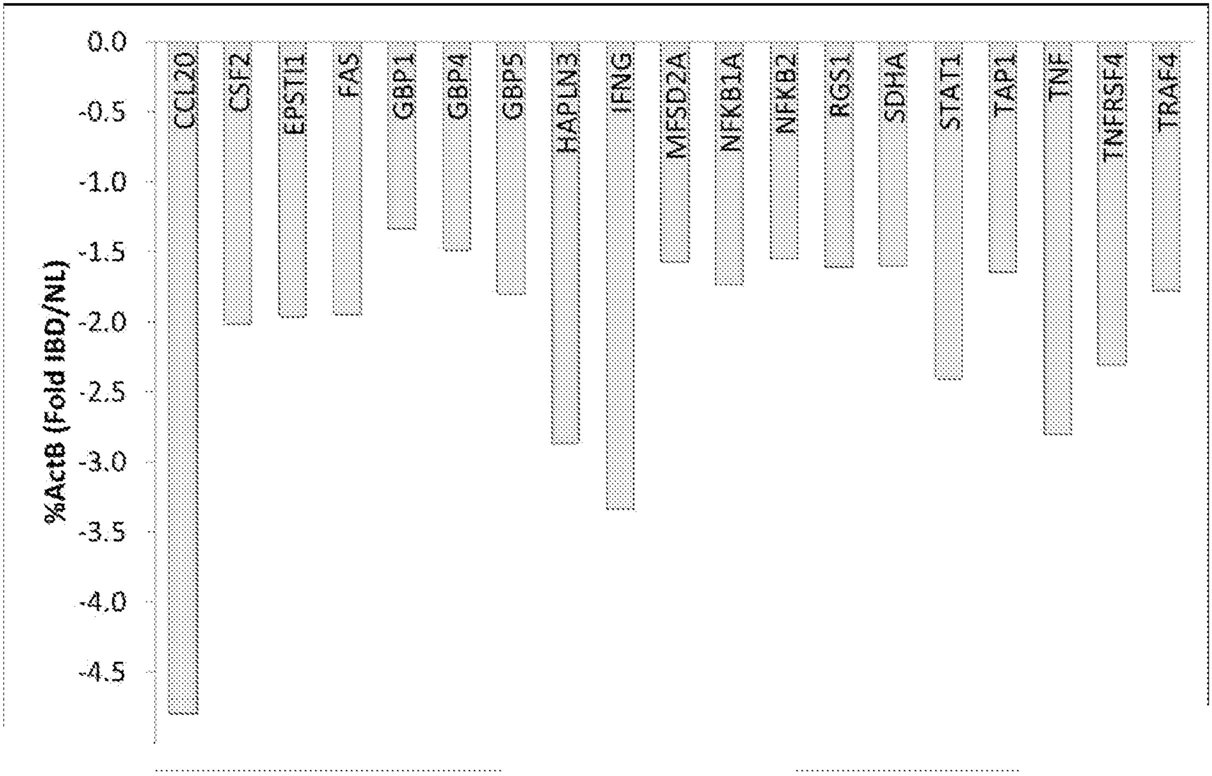

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GONSKY, Rebecca
DEEM, Richard

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