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(54) Title: METHODS FOR ASSESSING RESPONSIVENESS OF B-CELL LYMPHOMA TO TREATMENT WITH ANTI-CD40 ANTIBODIES

(57) Abstract: The invention provides methods and kits useful for predicting or assessing responsiveness of a patient having B-cell lymphoma to treatment with anti-CD40 antibodies.



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METHODS FOR ASSESSING RESPONSIVENESS OF B-CELL LYMPHOMA TO TREATMENT WITH ANTI-CD40 ANTIBODIES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of U.S. provisional application Serial No. 61/170,615, filed April 18, 2009, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present invention relates generally to the fields of predicting, assessing, aiding assessment of responsiveness of a patient with B-cell lymphoma to treatment with anti-CD40 antibodies, and methods for treating individuals identified as candidates for the anti-CD40 antibody treatment.

BACKGROUND

[0003] CD40 is a type I transmembrane protein of the tumor necrosis receptor superfamily. CD40 is an important molecule involved in B-cell proliferation and differentiation, immunoglobulin isotype switching, and cell viability. Receptor signaling is initiated by the binding of CD40 to the CD40 ligand (CD40L or CD154), which is primarily expressed on activated CD4+ T cells.

[0004] On normal cells, CD40 is expressed on cells with high proliferative potential, including hematopoietic progenitors, epithelial and endothelial cells, and all antigen-presenting cells (dendritic cells, activated B lymphocytes, and activated monocytes). CD40 is highly expressed on several types of B-cell hematologic malignancies including multiple myeloma, non-Hodgkin's lymphoma (NHL), and chronic lymphocytic leukemia (CLL). The high prevalence of CD40 expression on B-cell malignancies makes it an attractive potential tumor target for antibody-based cancer therapy. CD40 is also expressed on a majority of bladder cancers and a significant percentage of other solid tumors, including head and neck cancers, renal cell carcinomas, ovarian and lung cancer.

[0005] Anti-CD40 antibodies and their uses for treating B cell hematologic malignancies have been described. See, *e.g.*, US Pat. 6,946,129; 6,843,989; 6,838,261; WO 2000/075348; US-2002-0197256; WO 2006/128103; and WO 2007/075326. It has been shown that a humanized anti-CD40 antibody induces growth inhibition and apoptosis of CD40-positive cells in a subset of hematologic tumor cell lines through direct signal transduction. WO 2006/128103; WO 2007/075326. Furthermore, the humanized anti-CD40 antibody kills

tumor cells via immune effector functions, including antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). In vivo, using xenograft models of multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL), the anti-CD40 antibody suppresses tumor growth and improves survival in severe combined immunodeficient (SCID) mice. Comparison of the anti-CD40 antibody to rituximab (Genentech, Inc.) in several models revealed anti-tumor activity of the anti-CD40 antibody was at least as effective as rituximab. Clinical trials were initiated to test the humanized anti-CD40 antibody in patients with relapsed and refractory multiple myeloma (MM), relapsed non-Hodgkin's lymphoma (NHL), chronic lymphocytic lymphoma (CLL), or in relapsed diffuse large B cell lymphoma (DLBCL).

[0006] Although it has been shown anti-CD40 antibodies can induce growth inhibition and apoptosis of CD40-positive cells and may have anti-tumor activity in various types of B cell lymphoma patients, not all B lymphoma cells are sensitive to anti-CD40 antibody mediated cell death. There remains a need to identify one or more predictive markers for the responsiveness of B-cell lymphoma patients to an anti-CD40 antibody therapy.

[0007] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

[0007a] It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

SUMMARY OF THE INVENTION

[0008] The invention provides methods and compositions for predicting, assessing or aiding assessment of responsiveness of a subject having a type of B-cell lymphoma to treatment with an anti-CD40 antibody.

[0008a] In a first aspect, the invention provides a method for predicting responsiveness of a subject having B-cell lymphoma to an anti-CD40 antibody treatment, comprising the steps of: (a) measuring expression levels of RNA transcripts of marker genes in a sample comprising B lymphoma cells obtained from the subject, wherein said marker genes comprise BCL6, IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7; and (b) classifying the subject as a responsive or a non-responsive subject using a K-nearest neighbors analysis based on the expression level of said one or more marker genes in the sample from the subject and reference samples with

known classes. In some embodiments, said classification is determined using a weighted K-nearest neighbors analysis. In some embodiments, said classification is determined using an unweighted K-nearest neighbors analysis. In some embodiments, the classification of the subject in step (b) is carried out by (1) determining parameter K (i.e., number of nearest neighbors); (2) calculating the difference between the measured expression level of the marker genes in the sample from the subject and the expression level of the respective marker genes in each reference sample; (3) determining the nearest reference samples by selecting those samples with the smallest weighted average of the absolute differences (WAAD) between the sample from the subject and the reference sample; and (4) determining the class of the subject based on the known classes of the K-nearest reference samples. In some embodiments, K is determined using cross-validation with clinical trial samples. In some embodiments, K is 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13. In some embodiments, the reference samples are samples comprising B lymphoma cells obtained from subjects whose responsiveness to the anti-CD40 antibody treatment has been tested or is known. In some embodiments, the reference samples comprise the same type of B lymphoma cells as the sample from the subject whose responsiveness to the anti-CD40 antibody treatment is predicted or assessed. In some embodiments, expression levels of at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, at least fourteen, or all fifteen marker genes of BCL6, IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7 are measured and used for classifying the subject. In some embodiments, expression levels of BCL6, IFITM1, CD22, IGF1R, CD44, EPDR1, and UAP1 are measured and used in classifying the subject. In some embodiments, the measured expression level is normalized.

[0008b] In a second aspect, the invention provides a kit when used in the method of the first aspect for predicting responsiveness of a subject having B-cell lymphoma to an anti-CD40 antibody treatment, the kit comprising reagents for measuring the expression levels of the RNA transcripts of marker genes in a sample comprising B lymphoma cells from the subject, and optionally instructions for classifying the subject as a responsive or non-responsive subject using a K-nearest neighbors analysis based on the expression levels of the RNA transcripts of said marker genes in the sample from the subject and reference samples with known classes, wherein said marker genes comprise BCL6, IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7.

[0009] Also disclosed are methods for assessing or aiding assessment of responsiveness of a subject having a B-cell lymphoma to treatment with an anti-CD40 antibody, comprising comparing a measured expression level of at least one marker gene selected from the group consisting of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B in a B-cell lymphoma sample from the subject to a reference level.

[0010] Also disclosed are methods for predicting responsiveness or monitoring treatment/responsiveness to an anti-CD40 antibody treatment in a subject having a B-cell lymphoma, comprising comparing a measured expression level of at least one marker gene selected from the group consisting of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B in a B-cell lymphoma sample from the subject to a reference level.

[0011] Also disclosed are methods for predicting, assessing or aiding assessment of responsiveness of a subject having a B-cell lymphoma to an anti-CD40 antibody treatment, comprising the steps of: (a) measuring the expression level of one or more marker genes in a sample comprising B lymphoma cells obtained from said subject, wherein said one or more marker genes are selected from the group consisting of IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, PUS7, and BCL6; and (b) predicting whether the subject is likely to respond to the anti-CD40 antibody treatment based on the measured expression level of said one or more marker genes from step (a). In some embodiments, expression levels of at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, at least fourteen, or fifteen marker genes from the group are measured and used for the prediction, assessment, or aiding assessment. In some embodiments, the prediction, assessment, or aiding assessment is determined by comparing the measured expression level of one or more marker genes to a reference level. In some embodiments, a reference level is a value or a range determined based on the measured expression level of the corresponding marker gene in samples comprising the B lymphoma cells from subjects having tumor volume increased or decreased after the anti-CD40 antibody treatment. In some embodiments, samples from subjects for reference level determination comprise the same type of B lymphoma cells as the sample from the subject whose responsiveness to the anti-CD40 antibody treatment is predicted. In some embodiments, the responsiveness is predicted or assessed using the sensitivity index value determined based on

the measured expression level of one or more of the marker genes. In some embodiments, the responsiveness is predicted or assessed by classifying the subject using a K-nearest neighbors analysis described herein.

[0012] Also disclosed are methods for preparing a personalized genomics profile for a subject having B-cell lymphoma comprising the steps of: (a) determining the expression level of one or more marker genes selected from the group consisting of IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, PUS7, and BCL6 in a sample comprising B lymphoma cells obtained from the subject; and (b) generating a report summarizing the expression level of one or more marker genes obtained in step (a). In some embodiments, expression levels of at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, at least fourteen, or fifteen marker genes from the group are measured and used for generating the report for the personalized genomics profile. In some embodiments, the report includes a recommendation for an anti-CD40 antibody treatment for the subject. In some embodiments, the recommendation is determined by comparing the measured expression level of the marker genes to a reference level. In some embodiments, a reference level is a value or a range determined based on the measured expression level of the corresponding marker gene in samples comprising the B lymphoma cells from subjects having tumor volume increased or decreased after the anti-CD40 antibody treatment. In some embodiments, the recommendation is determined by the sensitivity index value determined based on the measured expression level of the marker genes. In some embodiments, the recommendation is determined by classifying the subject using a K-nearest neighbors analysis described herein.

[0013] Also disclosed are methods for predicting, assessing or aiding assessment of responsiveness of a subject having a B-cell lymphoma to an anti-CD40 antibody treatment, comprising the steps of: (a) measuring the expression level at least two marker genes selected from the group consisting of IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, PUS7, and BCL6 in a sample comprising B lymphoma cells from the subject; (b) calculating sensitivity index value (SI) based on the measured expression level of the marker genes in step (a) by the following equation:

$$SI = \sum_{j=1}^p \beta_j \frac{x_j - \hat{\mu}_j}{\sqrt{\hat{\sigma}_j^2}}$$

wherein the expression level of at least one marker gene having a positive correlation value and at least one marker gene having a negative correlation value shown in Table 4 is measured;

wherein (i) β_j is the coefficient value for each marker genes measured; (ii) p is the number of marker genes measured; (iii) x_i is transformed, normalized expression level for the sample from the subject for the expression level of each marker measured; and (iv) μ_j and σ_j are means and standard deviations for each marker gene measured; wherein β_j , μ_j and σ_j are determined from patient samples comprising the B lymphoma cells. In some embodiments, a value equals or greater than zero for the sensitivity index indicates that the subject is likely to respond to the anti-CD40 antibody treatment, or wherein a value less than zero for the sensitivity index indicates that the subject is less likely to respond to the anti-CD40 antibody treatment. In some embodiments, the expression levels of at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, at least fourteen, or fifteen marker genes are measured and used for the sensitivity index calculation. In some embodiments, the expression level of IFITM1, RGS13, CD79B, CD22, BTG2, CD44, EPDR1, and UAP1 are measured and used for the sensitivity index calculation. In some embodiments, β_j , μ_j and σ_j are determined from patient samples have the same type of B lymphoma cells as the sample from subject whose responsiveness to the anti-CD40 treatment is predicted.

[0015] Also disclosed are methods for treating a subject having B-cell lymphoma, comprising administering an effective amount of an anti-CD40 antibody to the subject, wherein the responsiveness of the B-cell lymphoma in the subject has been assessed by the methods described herein. Also disclosed are methods for treating a subject having B-cell lymphoma, comprising a) selecting a subject for an anti-CD40 antibody treatment by comparing a measured expression level of at least one marker gene selected from the group consisting of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B in a B-cell lymphoma sample from the subject to a reference level to assess if the B-cell lymphoma in the subject is suitable for the anti-CD40 antibody treatment; and administering an effective amount of the anti-CD40 antibody to the subject. In another aspect, the invention provides methods for treating a subject having B-cell lymphoma, comprising a) selecting a subject for an anti-CD40 antibody treatment if the

subject is classified as a responsive subject using a K-nearest neighbors analysis based on the measured expression level of one or more marker genes selected from the group consisting of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B in a B-cell lymphoma sample from the subject and reference samples with known classes; and administering an effective amount of the anti-CD40 antibody to the subject.

[0016] In some embodiments, the reference level is a measured expression level of the marker gene in a different B-cell lymphoma sample. In some embodiments, said different B cell lymphoma sample comprises B lymphoma cells that are resistant to an anti-CD40 antibody induced cell death.

[0017] In some embodiments, the measured expression level of the marker gene and/or the reference level are normalized.

[0018] In some embodiments, measured expression levels of at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, at least fourteen, or fifteen genes selected from the group consisting of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B in the B-cell lymphoma sample from the subject are compared to one or more reference levels.

[0019] In some embodiments, the expression level is measured by detecting mRNA expression (e.g., real time quantitative reverse transcription PCR (qRT-PCR)) and/or by detecting protein expression (e.g., immunohistochemistry (IHC)). Probes and primers shown in Table 1 may be used in qRT-PCR.

[0020] In some embodiments, B-cell lymphoma is non-Hodgkin's lymphoma (NHL), including, but is not limited to, follicular lymphoma, relapsed follicular lymphoma, small lymphocytic lymphoma, mantle cell lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma, mycosis fungoides/Sezary syndrome, splenic marginal zone lymphoma, and diffuse large B-cell lymphoma (DLBCL). In some embodiments, B-cell lymphoma is selected from the group consisting of indolent lymphoma, aggressive lymphoma, and highly aggressive lymphoma. In some embodiments, B-cell lymphoma is relapsed and/or refractory lymphoma. In some embodiments, B-cell lymphoma is relapsed/refractory DLBCL.

[0021] In some embodiments, the anti-CD40 antibody treatment is a treatment with an agonist anti-CD40 antibody. In some embodiments, the agonist anti-CD40 antibody stimulates CD40 and enhances the interaction between CD40 and CD40 ligand. In some embodiments, the agonist anti-CD40 antibody stimulates CD40 but does not enhance or inhibits the interaction between CD40 and CD40 ligand. In some embodiments, the agonist anti-CD40 antibody comprises the heavy chain amino acid sequence shown in SEQ ID NO:1 and the light chain amino acid sequence shown in SEQ ID NO:2.

[0022] Also disclosed are kits comprising reagents for measuring expression levels of at least one marker gene selected from the group consisting of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B. In some embodiments, the kits comprise at least a pair of primers for amplifying by PCR at least one marker gene. For example, forward and reverse primers shown in Table 1 may be used. The kits may further comprise a surface having attached thereof probes for detecting the amplified gene products, such as a microarray and the invention contemplates and includes such surfaces. In some embodiments, the kits comprise at least a pair of primers and a probe for detecting expression level of one marker gene (such as UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B) by qRT-PCR. The kits may further comprise a pair of primers and a probe for detecting expression level of a reference gene by qRT-PCR. In some

embodiments, the kits comprise one or more antibodies that specifically recognize one or more proteins encoded by the marker gene. The kits may further comprise other reagents and/or instructions for carrying out any of the methods described herein.

[0023] It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present invention. These and other aspects of the invention will become apparent to one of skill in the art.

BRIEF DESCRIPTION OF THE FIGURES

[0024] Figure 1-1 to 1-26. GenBank sequences for some of the genes listed in Table 1. Nucleic acid sequences encoding mRNA of VNN2 (Figure 1-1: SEQ ID NO:258), RGS13 (Figure 1-2: SEQ ID NO:259), CD22 (Figure 1-3 and 1-4: SEQ ID NO:260), CD40 (Figure 1-5: SEQ ID NO:261), IFITM1 (Figure 1-6: SEQ ID NO:262), BCL6 (Figure 1-7 and 1-8: SEQ ID NO:263), EPDR1 (Figure 1-9: SEQ ID NO:264), IGF1R (Figure 1-10 to 1-13: SEQ ID NO:265), BTG2 (Figure 1-14 and 1-15: SEQ ID NO:266), LMO2 (Figure 1-16: SEQ ID NO:267), CD79B (Figure 1-17: SEQ ID NO:268), CD44 (Figure 1-18 and 1-19: SEQ ID NO:269), CTSC (Figure 1-20: SEQ ID NO:270), UAP1 (Figure 1-21: SEQ ID NO:271), PUS7 (Figure 1-22 and 1-23: SEQ ID NO:272), CD22 (Figure 1-24 and 1-25: SEQ ID NO:273), and RGS13 (Figure 1-26: SEQ ID NO:274).

[0025] Figure 2. Association of multivariate sensitivity index and percent change in tumor sum of the product of diameters (SPD) measurements for 21 patients in Clinical Trial 001. SPD percent change is determined by comparing the smallest post-baseline SPD to baseline SPD. Positive change indicates tumor volume increases, and negative change indicates tumor volume decreases. Weights (coefficients) used for the sensitivity index calculation are shown in Table 5. Larger multivariate sensitivity index values are associated with SPD decreases post-baseline (Sperman's Rho = -0.58; P=0.006).

[0026] Figure 3. Association of BCL6 expression and percent change in SPD measurements for 26 patients with DLBCL. SPD percent change was determined by comparing the smallest post-baseline SPD to baseline SPD. Positive change indicates tumor volume increases, and negative change indicates tumor volume decreases.

[0027] Figure 4. Use of mRNA expression levels of the marker genes to predict sensitivity to anti-CD40 Ab.1 treatment. SPD percent change was determined by comparing the smallest post-baseline SPD to baseline SPD. Positive change indicates tumor volume increases, and negative change indicates tumor volume decreases.

[0028] Figure 5. Progression-free survival for patients that had been classified as being responsive (Dx Positive) to the anti-CD40 Ab.1 treatment or non-responsive (Dx Negative) based on the mRNA expression levels of the marker genes.

DETAILED DESCRIPTION

[0029] The present invention is based on the discovery that certain genes are differentially expressed between B lymphoma cells that are sensitive to anti-CD40 antibody induced cell death and B lymphoma cells that are resistant to anti-CD40 induced cell death. Data from clinical trials described in Examples 1 and 2 indicate that the expression level of one or more of the fifteen genes UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B can be used to predict, assess or aid assessment of responsiveness to anti-CD40 antibody treatment (such as anti-CD40 Ab.1 treatment). Some of the differentially expressed genes between sensitive B lymphoma cells and resistant B lymphoma cells are the CD40 ligand downregulated pathway genes; and some are in the B-cell receptor signaling pathway. Accordingly, expression levels of one or more of these differentially expressed genes can be used for assessing or aiding assessment of responsiveness of a subject having B-cell lymphoma to treatment with anti-CD40 antibodies, predicting responsiveness of the subject to treatment with anti-CD40 antibodies, and monitoring treatment/responsiveness in the subject.

A. General Techniques

[0030] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, "Molecular Cloning: A Laboratory Manual", second edition (Sambrook et al., 1989); "Oligonucleotide Synthesis" (M. J. Gait, ed., 1984); "Animal Cell Culture" (R. I. Freshney, ed., 1987); "Methods in Enzymology" (Academic Press, Inc.); "Current Protocols in Molecular Biology" (F. M. Ausubel et al., eds., 1987, and periodic updates); "PCR: The Polymerase Chain Reaction", (Mullis et al., eds., 1994).

[0031] Primers, oligonucleotides and polynucleotides employed in the present invention can be generated using standard techniques known in the art.

[0032] 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. Singleton et al., Dictionary of Microbiology and Molecular Biology 2nd ed., J. Wiley & Sons (New York, N.Y. 1994), and March, Advanced Organic Chemistry Reactions, Mechanisms and Structure 4th ed., John Wiley & Sons (New York, N.Y. 1992), provide one skilled in the art with a general guide to many of the terms used in the present application.

B. Definitions

[0032a] In the claims which follow and in the description of the invention, except where the context requires otherwise due to express language or necessary implication, the word “comprise” or variations such as “comprises” or “comprising” is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

[0033] As used herein, the terms “a subject having a B-cell lymphoma” and “B-cell lymphoma patient” refer to a subject who has been diagnosed with a type of B-cell lymphoma or has been given a probable diagnosis of a type of B-cell lymphoma.

[0034] The term “biomarker” or “marker” as used herein refers generally to a molecule, including a gene, protein, carbohydrate structure, or glycolipid, the expression of which in or on a mammalian tissue or cell or secreted can be detected by known methods (or methods disclosed herein) and is predictive or can be used to predict (or aid prediction) for a mammalian cell’s or tissue’s sensitivity to, and in some embodiments, to predict (or aid prediction) an individual’s responsiveness to treatment regimes based on anti-CD40 antibodies.

[0035] The term “sample”, as used herein, refers to a composition that is obtained or derived from a subject of interest that contains a cellular and/or other molecular entity that is to be characterized and/or identified, for example based on physical, biochemical, chemical and/or physiological characteristics. For example, the phrase “disease sample” and variations thereof refers to any sample obtained from a subject of interest that would be expected or is known to contain the cellular and/or molecular entity that is to be characterized.

[0036] By “tissue or cell sample” is meant a collection of similar cells obtained from a tissue of a subject or patient. The source of the tissue or cell sample may be solid tissue as from a fresh, frozen and/or preserved organ or tissue sample or biopsy or aspirate; blood or any blood constituents; bodily fluids such as cerebral spinal fluid, amniotic fluid, peritoneal fluid, or interstitial fluid; cells from any time in gestation or development of the subject. The tissue sample may also be primary or cultured cells or cell lines. Optionally, the tissue or cell

sample is obtained from a disease tissue/organ. The tissue sample may contain compounds which are not naturally intermixed with the tissue in nature such as preservatives, anticoagulants, buffers, fixatives, nutrients, antibiotics, or the like.

[0037] For the purposes herein a “section” of a tissue sample is meant a single part or piece of a tissue sample, *e.g.* a thin slice of tissue or cells cut from a tissue sample. It is understood that multiple sections of tissue samples may be taken and subjected to analysis according to

the present invention, provided that it is understood that the present invention comprises a method whereby the same section of tissue sample is analyzed at both morphological and molecular levels, or is analyzed with respect to both protein and nucleic acid.

[0038] As used herein, a “B-cell lymphoma sample” or a “sample comprising B lymphoma cells” is a tissue or cell sample containing B lymphoma cells from a subject or a patient that have been diagnosed with a type of B-cell lymphoma.

[0039] As used herein, method for “aiding assessment” refers to methods that assist in making a clinical determination (*e.g.*, responsiveness of a B-cell lymphoma to treatment with anti-CD40 antibodies), and may or may not be conclusive with respect to the definitive assessment.

[0040] A “subject” or an “individual” is a mammal, more preferably a human. Mammals include, but are not limited to, humans, primates, farm animal, sport animals, rodents, and pets (*e.g.*, dogs and cats).

[0041] As used herein, a “reference value” can be an absolute value; a relative value; a value that has an upper and/or lower limit; a range of values; an average value; a median value; a mean value; or a value as compared to a particular control or baseline value.

[0042] The term “array” or “microarray”, as used herein refers to an ordered arrangement of hybridizable array elements, such as polynucleotide probes (*e.g.*, oligonucleotides) and antibodies, on a substrate. The substrate can be a solid substrate, such as a glass slide, or a semi-solid substrate, such as nitrocellulose membrane. The nucleotide sequences can be DNA, RNA, or any permutations thereof.

[0043] “Amplification,” as used herein, generally refers to the process of producing multiple copies of a desired sequence. “Multiple copies” means at least 2 copies. A “copy” does not necessarily mean perfect sequence complementarity or identity to the template sequence. For example, copies can include nucleotide analogs such as deoxyinosine, intentional sequence alterations (such as sequence alterations introduced through a primer comprising a sequence that is hybridizable, but not complementary, to the template), and/or sequence errors that occur during amplification.

[0044] Expression/amount of a gene or biomarker in a first sample is at a level “greater than” the level in a second sample if the expression level/amount of the gene or biomarker in the first sample is at least about 1.5X, 1.75X, 2X, 3X, 4X, 5X, 6X, 7X, 8X, 9X or 10X the expression level/amount of the gene or biomarker in the second sample. Expression levels/amounts can be determined based on any suitable criterion known in the art, including

but not limited to mRNA, cDNA, proteins, protein fragments and/or gene copy. Expression levels/amounts can be determined qualitatively and/or quantitatively.

[0045] "Polynucleotide," or "nucleic acid," as used interchangeably herein, refer to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. Other types of modifications include, for example, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, cabamates, etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, ply-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotide(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping groups moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-2'-O- allyl, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, α - anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S("thioate"), P(S)S("dithioate"), "(O)NR₂("amidate"), P(O)R, P(O)OR', CO or CH₂("formacetal"), in which each R or R' is independently H or substituted or unsubstituted alkyl

(1-20 C) optionally containing an ether (--O--) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.

[0046] "Oligonucleotide," as used herein, generally refers to short, generally single stranded, generally synthetic polynucleotides that are generally, but not necessarily, less than about 200 nucleotides in length. The terms "oligonucleotide" and "polynucleotide" are not mutually exclusive. The description above for polynucleotides is equally and fully applicable to oligonucleotides.

[0047] A "primer" is generally a short single stranded polynucleotide, generally with a free 3'-OH group, that binds to a target potentially present in a sample of interest by hybridizing with a target sequence, and thereafter promotes polymerization of a polynucleotide complementary to the target. A "pair of primers" refer to a 5' primer and a 3' primer that can be used to amplify a portion of a specific target gene.

[0048] The term "3'" generally refers to a region or position in a polynucleotide or oligonucleotide 3' (downstream) from another region or position in the same polynucleotide or oligonucleotide. The term "5'" generally refers to a region or position in a polynucleotide or oligonucleotide 5' (upstream) from another region or position in the same polynucleotide or oligonucleotide.

[0049] The phrase "gene amplification" refers to a process by which multiple copies of a gene or gene fragment are formed in a particular cell or cell line. The duplicated region (a stretch of amplified DNA) is often referred to as "amplicon." Usually, the amount of the messenger RNA (mRNA) produced, i.e., the level of gene expression, also increases in the proportion of the number of copies made of the particular gene expressed.

[0050] "Detection" includes any means of detecting, including direct and indirect detection.

[0051] The term "prediction" is used herein to refer to the likelihood that a patient will respond either favorably or unfavorably to a drug or set of drugs. In one embodiment, the prediction relates to the extent of those responses. In one embodiment, the prediction relates to whether and/or the probability that a patient will survive or improve following treatment, for example treatment with a particular therapeutic agent, and for a certain period of time without disease recurrence. The predictive methods of the invention can be used clinically to make treatment decisions by choosing the most appropriate treatment modalities for any particular patient. The predictive methods of the present invention are valuable tools in predicting if a patient is likely to respond favorably to a treatment regimen, such as a given therapeutic regimen, including for example, administration of a given therapeutic agent or

combination, surgical intervention, steroid treatment, etc., or whether long-term survival of the patient, following a therapeutic regimen is likely.

[0052] The term "long-term" survival is used herein to refer to survival for at least 1 year, 5 years, 8 years, or 10 years following therapeutic treatment.

[0053] "Patient response" can be assessed using any endpoint indicating a benefit to the patient, including, without limitation, (1) inhibition, to some extent, of disease progression, including slowing down and complete arrest; (2) reduction in the number of disease episodes and/or symptoms; (3) reduction in lesional size; (4) inhibition (i.e., reduction, slowing down or complete stopping) of disease cell infiltration into adjacent peripheral organs and/or tissues; (5) inhibition (i.e. reduction, slowing down or complete stopping) of disease spread; (6) relief, to some extent, of one or more symptoms associated with the disorder; (7) increase in the length of disease-free presentation following treatment; and/or (8) decreased mortality at a given point of time following treatment.

[0054] The term "antibody" is used in the broadest sense and specifically covers monoclonal antibodies (including full length monoclonal antibodies), multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired biological activity or function.

[0055] "Antibody fragments" comprise a portion of a full length antibody, generally the antigen binding or variable region thereof. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

[0056] "Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

[0057] The term "monoclonal antibody" as used herein refers to an antibody from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope(s), except for possible variants that may arise during production of the monoclonal antibody, such variants generally being present in minor amounts. Such monoclonal antibody typically includes an antibody

comprising a polypeptide sequence that binds a target, wherein the target-binding polypeptide sequence was obtained by a process that includes the selection of a single target binding polypeptide sequence from a plurality of polypeptide sequences. For example, the selection process can be the selection of a unique clone from a plurality of clones, such as a pool of hybridoma clones, phage clones or recombinant DNA clones. It should be understood that the selected target binding sequence can be further altered, for example, to improve affinity for the target, to humanize the target binding sequence, to improve its production in cell culture, to reduce its immunogenicity *in vivo*, to create a multispecific antibody, *etc.*, and that an antibody comprising the altered target binding sequence is also a monoclonal antibody of this invention. In contrast to polyclonal antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. In addition to their specificity, the monoclonal antibody preparations are advantageous in that they are typically uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by a variety of techniques, including, for example, the hybridoma method (*e.g.*, Kohler *et al.*, *Nature*, 256:495 (1975); Harlow *et al.*, *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling *et al.*, in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681, (Elsevier, N.Y., 1981)), recombinant DNA methods (see, *e.g.*, U.S. Patent No. 4,816,567), phage display technologies (see, *e.g.*, Clackson *et al.*, *Nature*, 352:624-628 (1991); Marks *et al.*, *J. Mol. Biol.*, 222:581-597 (1991); Sidhu *et al.*, *J. Mol. Biol.* 338(2):299-310 (2004); Lee *et al.*, *J. Mol. Biol.* 340(5):1073-1093 (2004); Fellouse, *Proc. Nat. Acad. Sci. USA* 101(34):12467-12472 (2004); and Lee *et al.*, *J. Immunol. Methods* 284(1-2):119-132 (2004), and technologies for producing human or human-like antibodies in animals that have parts or all of the human immunoglobulin loci or genes encoding human immunoglobulin sequences (see, *e.g.*, WO 1998/24893; WO 1996/34096; WO 1996/33735; WO 1991/10741; Jakobovits *et al.*, *Proc. Natl. Acad. Sci. USA*, 90:2551 (1993); Jakobovits *et al.*, *Nature*, 362:255-258 (1993); Bruggemann *et al.*, *Year in Immuno.*, 7:33 (1993); U.S. Patent Nos. 5,545,806; 5,569,825; 5,591,669 (all of GenPharm); 5,545,807; WO 1997/17852; U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016; Marks *et al.*, *Bio/Technology*, 10: 779-783 (1992); Lonberg *et al.*, *Nature*, 368: 856-859 (1994); Morrison, *Nature*, 368:

812-813 (1994); Fishwild *et al.*, *Nature Biotechnology*, 14: 845-851 (1996); Neuberger, *Nature Biotechnology*, 14: 826 (1996); and Lonberg and Huszar, *Intern. Rev. Immunol.*, 13: 65-93 (1995).

[0058] The monoclonal antibodies herein specifically include "chimeric" antibodies. "Chimeric" antibodies (immunoglobulins) have a portion of the heavy and/or light chain identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; and Morrison *et al.*, *Proc. Natl. Acad. Sci. USA* 81:6851-6855 (1984)). Humanized antibody as used herein is a subset of chimeric antibodies.

[0059] "Humanized" forms of non-human (*e.g.*, murine) antibodies are chimeric antibodies which contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient or acceptor antibody) in which hypervariable region residues of the recipient are replaced by hypervariable region residues from a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues which are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance such as binding affinity. Generally, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence although the FR regions may include one or more amino acid substitutions that improve binding affinity. The number of these amino acid substitutions in the FR are typically no more than 6 in the H chain, and in the L chain, no more than 3. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones *et al.*, *Nature* 321:522-525 (1986); Reichmann *et al.*, *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992).

[0060] A “human antibody” is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human and/or has been made using any of the known techniques for making human antibodies. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues.

[0061] An “affinity matured” antibody is one with one or more alterations in one or more CDRs/HVRs thereof which result in an improvement in the affinity of the antibody for antigen, compared to a parent antibody which does not possess those alteration(s). Preferred affinity matured antibodies will have nanomolar or even picomolar affinities for the target antigen. Affinity matured antibodies are produced by procedures known in the art. Marks *et al. Bio/Technology* 10:779-783 (1992) describes affinity maturation by VH and VL domain shuffling. Random mutagenesis of CDR/HVR and/or framework residues is described by: Barbas *et al. Proc Nat. Acad. Sci, USA* 91:3809-3813 (1994); Schier *et al. Gene* 169:147-155 (1995); Yelton *et al. J. Immunol.* 155:1994-2004 (1995); Jackson *et al., J. Immunol.* 154(7):3310-9 (1995); and Hawkins *et al, J. Mol. Biol.* 226:889-896 (1992).

[0062] The term “Fc region” is used to define the C-terminal region of an immunoglobulin heavy chain which may be generated by papain digestion of an intact antibody. The Fc region may be a native sequence Fc region or a variant Fc region. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an amino acid residue at about position Cys226, or from about position Pro230, to the carboxyl-terminus of the Fc region. The Fc region of an immunoglobulin generally comprises two constant domains, a CH2 domain and a CH3 domain, and optionally comprises a CH4 domain. By “Fc region chain” herein is meant one of the two polypeptide chains of an Fc region.

[0063] Antibody “effector functions” refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (*e.g.* B cell receptor); and B cell activation.

[0064] “Antibody-dependent cell-mediated cytotoxicity” or “ADCC” refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells (*e.g.* Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. The antibodies “arm” the cytotoxic cells and are absolutely

required for such killing. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol* 9:457-92 (1991). To assess ADCC activity of a molecule of interest, an *in vitro* ADCC assay, such as that described in US Patent No. 5,500,362 or 5,821,337 or Presta U.S. Patent No. 6,737,056 may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, e.g., in a animal model such as that disclosed in Clynes *et al. PNAS (USA)* 95:652-656 (1998).

[0065] "Treating" or "treatment" or "alleviation" refers to therapeutic treatment wherein the object is to slow down (lessen) if not cure the targeted pathologic condition or disorder or prevent recurrence of the condition. A subject is successfully "treated" for the B cell malignancy if, after receiving a therapeutic amount of a CD40 binding antibody, the subject shows observable and/or measurable reduction in or absence of one or more signs and symptoms of the particular disease. For example, significant reduction in the number of cancer cells or absence of the cancer cells; reduction in the tumor size; inhibition (*i.e.*, slow to some extent and preferably stop) of tumor metastasis; inhibition, to some extent, of tumor growth; increase in length of remission, and/or relief to some extent, one or more of the symptoms associated with the specific cancer; reduced morbidity and mortality, and improvement in quality of life issues. Reduction of the signs or symptoms of a disease may also be felt by the patient. Treatment can achieve a complete response, defined as disappearance of all signs of cancer, or a partial response, wherein the size of the tumor is decreased, preferably by more than 50 percent, more preferably by 75%. A patient is also considered treated if the patient experiences stable disease. In one criterion, the antibodies of the invention achieve > 95% peripheral blood B cell depletion and the B cells return to 25% of baseline. In some embodiments, treatment with the anti-CD40 antibodies is effective to result in the cancer patients being progression-free in the cancer 3 months after treatment, preferably 6 months, more preferably one year, even more preferably 2 or more years post treatment. These parameters for assessing successful treatment and improvement in the disease are readily measurable by routine procedures familiar to a physician of appropriate skill in the art.

[0066] The term "non-Hodgkin's lymphoma" or "NHL", as used herein, refers to a cancer of the lymphatic system other than Hodgkin's lymphomas. Hodgkin's lymphomas can

generally be distinguished from non-Hodgkin's lymphomas by the presence of Reed-Sternberg cells in Hodgkin's lymphomas and the absence of said cells in non-Hodgkin's lymphomas.

[0067] An "effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result. A "therapeutically effective amount" of a therapeutic agent may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the therapeutic agent are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically but not necessarily, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

[0068] The term "housekeeping gene" refers to a group of genes that codes for proteins whose activities are essential for the maintenance of cell function. These genes are typically similarly expressed in all cell types.

[0069] By "correlate" or "correlating" is meant comparing, in any way, the performance and/or results of a first analysis or protocol with the performance and/or results of a second analysis or protocol. For example, one may use the results of a first analysis or protocol in carrying out a second protocols and/or one may use the results of a first analysis or protocol to determine whether a second analysis or protocol should be performed. With respect to the embodiment of gene expression analysis or protocol, one may use the results of the gene expression analysis or protocol to determine whether a specific therapeutic regimen should be performed.

[0070] The word "label" when used herein refers to a compound or composition which is conjugated or fused directly or indirectly to a reagent such as a nucleic acid probe or an antibody and facilitates detection of the reagent to which it is conjugated or fused. The label may itself be detectable (*e.g.*, radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

[0071] As used herein, "a", "an", and "the" can mean singular or plural (*i.e.*, can mean one or more) unless indicated otherwise.

[0072] It is understood that aspect and embodiments of the invention described herein include “comprising,” “consisting,” and “consisting essentially of” aspects and embodiments.

C. Methods of the Invention

[0073] The invention provides methods for assessing or aiding assessment of responsiveness of a subject having B-cell lymphoma to treatment with an anti-CD40 antibody. The invention also provides methods for predicting responsiveness or monitoring treatment/responsiveness to an anti-CD40 antibody treatment in a subject having B-cell lymphoma. The invention provides methods for selecting a subject having B-cell lymphoma for treatment with an anti-CD40 antibody and treating the subject with an anti-CD40 antibody treatment. In some embodiments, the methods comprise measuring the expression level of one or more marker genes selected from the group consisting of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B in a sample comprising B lymphoma cells obtained from the subject; and predicting, assessing, or aiding assessment of responsiveness of the subject to an anti-CD40 antibody treatment based on the measure expression level of said one or more marker genes. In some embodiments, the methods comprise comparing the measured expression level of at least one marker gene selected from UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B in a B-cell lymphoma sample from the subject to a reference level for the respective marker gene. In some embodiments, the responsiveness is predicted or assessed using the sensitivity index value determined based on the measured expression level of one or more of the marker genes. In some embodiments, the responsiveness is predicted or assessed by classifying the subject using a K-nearest neighbors analysis described herein.

[0074] The methods of the present invention are useful for clinicians to identify patients with B-cell lymphoma for treatment with an anti-CD40 antibody, aid in patient selection during the course of development of anti-CD40 antibody therapy, predict likelihood of success when treating an individual patient with a particular treatment regimen, assess and monitor disease progression, monitor treatment efficacy, and determine prognosis for individual patients. Any of these embodiments are included in this invention.

[0075] In some embodiments, B-cell lymphoma is non-Hodgkin's lymphoma (NHL), including, but is not limited to, follicular lymphoma, relapsed follicular lymphoma, small lymphocytic lymphoma, mantle cell lymphoma, marginal zone lymphoma,

lymphoplasmacytic lymphoma, mycosis fungoides/Sezary syndrome, splenic marginal zone lymphoma, and diffuse large B-cell lymphoma.

[0076] In some embodiments, B-cell lymphoma is indolent. In some embodiments, B-cell lymphoma is aggressive. In some embodiments, B-cell lymphoma is highly aggressive. In some embodiments, indolent B-cell lymphoma is follicular lymphoma, marginal zone lymphoma, or small lymphocytic lymphoma. In some embodiments, indolent B-cell lymphoma is follicular lymphoma.

Marker genes

[0077] The expression level of one or more of the marker genes in a B-cell lymphoma sample may be used in the methods of the invention, such as to predict, assess or aid assessment of responsiveness of the B-cell lymphoma to treatment with an anti-CD40 antibody. In some embodiments, the expression level of one or more of the marker genes relative to a reference level is used in the methods of the invention.

[0078] Using the expression level of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B for predicting, assessing or aiding assessment of responsiveness to an anti-CD40 antibody treatment is shown in Examples 1 and 2. Expression levels of one or more of these genes are used in the methods of the invention. In some embodiments, expression levels of at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, at least fourteen, or fifteen genes selected from UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B are measured and used in the methods of the invention.

[0079] Genes (including sequences) used as markers herein are known in the art. For example, examples of GenBank accession numbers for human genes are VNN2 (NM_004665; NM_078488; AJ132100; D89974; BC064641; CR609799; BC126145; BC126147; and AB026705); RGS13 (NM_002927; NM_144766; BT006929; BC056866; AY562947; CR536532; CR610389; CR599001; BC016667; AF493935; BC036950; and AF030107); CD22 (NM_001771; AK026467; BC109306; BC109307; AK225694; AK225625; X52785; and X59350); LRRC8A (AY143166; BC051322; AK123611; AY358286; NM_019594; XM_026998; AK001199; AB037858; CR619692; CR619448; AK024649; BC000775; AK027495; and AK074723); CD40 (NM_001250; NM_152854; BC064518; AY225405; CR619622; CR608994; CR605787; AB209660; AK222896; AJ300189; BT019901; and BC012419); IFITM1 (NM_003641; BC000897; BT007173;

BT009859; CR456894; CR541874; CR604902; X57351; X84958; NM_006435; BC009696; X02490; and J04164); SMN1 (NM_000344; BC062723; CR611445; CR593735; BC000908; NM_022874; BC015308; and U18423); PRKCA (NM_002737; AB209475; BC109274; BC109273; AF035594; BC053321; BX648954; AK125425; BC062759; BC071767; BC103691; BC101403; BC107592; AY633609; BC122530; BC015855; AF086287; AF035595; M22199; and X52479); EPDR1 (DQ914439; AY027862; NM_017549; AJ250475; AF202051; CR624676; CR596656; NM_016616; BC000686; BC018299; AF305596; and BC036816); PRPSAP2 (NM_002767; AB007851; BX648850; AK126398; CR457082; BC101672; BC101670; and BC106050); IGF1R (NM_000875; NM_015883; AY429545; CR624013; BC078157; BC088377; BC107089; BC111046; BC113610; BC113612; BC010607; X04434 M24599; and U09023); BTG2 (NM_006763; CR606002; CR604962; CR595352; CR591042; BC105948; BC105949; U72649; and Y09943); LMO2 (BC042426; NM_005574; BC073973; AK127915; CR625714; CR614368; CR604507; AF257211; BC034041; BC035607; and X61118); YIPF3 (AL050274; AK000946; CR533541; CR623137; CR622890; CR622532; CR621993; CR619816; CR619437; CR619054; CR618212; CR616987; CR616384; CR615623; CR615153; CR615118; CR612415; CR611748; CR611260; CR610983; CR610470; CR607768; CR606024; CR603408; CR603202; CR602267; CR601987; CR599615; CR598162; CR597677; CR596581; CR596249; CR595236; CR592266; CR590752; CR590349; NM_015388; AK021433; AK021655; AK022757; BC019297; and AF162672); and BCL6 (NM_001706; NM_138931; BX649185; U00115; BC142705; BC146796; BC150184; AL713713; AK090890; AL832990; and Z21943). GenBank accession numbers for marker genes are also listed in Table 1.

[0080] The nucleic acid sequence of some of the genes are shown in Figure 1 (1-1 to 1-26).

Reference levels

[0081] The measured expression level of one or more marker genes in a B-cell lymphoma sample is compared to a reference level. In some embodiments, the reference level is the expression level of a gene the expression level of which does not change (does not change significantly) among different type of B-cell lymphomas, for example, between B-cell lymphoma sensitive to anti-CD40 antibody and B-cell lymphoma resistant to anti-CD40 antibody. In some embodiments, expression levels of one or more housekeeping genes (such as genes shown in Tables 8 and 9 of WO 2009/062125) are used as reference levels.

[0082] In some embodiments, the measured expression level of the marker gene is normalized using the reference level. In some embodiments, the normalized expression level of the marker gene is calculated as a ratio of or difference between the marker gene and reference expression levels, on the original or on a log scale, respectively.

[0083] The reference genes may be selected as specific normalizing counterparts to the marker genes. Reference genes were selected for high mean expression and low variance in B cell lymphoma samples. In addition, reference genes were selected to have similar variance between replicated expression measurements of individual cell lines relative to variance between expression measurements of biologically distinct cell lines. In addition, reference genes were selected to have low statistical association with one or more markers.

[0084] In some embodiments, the reference level is a measured expression level of the marker gene in a different B-cell lymphoma sample. In some embodiments, the different B cell lymphoma sample comprises B lymphoma cells that are resistant to an anti-CD40 antibody induced cell death.

[0085] In some embodiments, the reference level is determined based on the expression level of the corresponding marker gene in samples comprising B lymphoma cells from subjects having tumor volume increased after the anti-CD40 antibody treatment and/or having tumor volume decreased after the anti-CD40 antibody treatment. In some embodiments, the samples from subjects for reference level determination comprise the same type of B lymphoma cells as the sample from the subject whose responsiveness to the anti-CD40 antibody treatment is predicted or assessed. In some embodiments, the same method (e.g., qRT-PCR) and/or reagents (e.g., primers and probes) are used for measuring expression level of the marker genes in the sample and measuring expression level of the corresponding marker genes in the reference samples.

Measuring expression levels

[0086] The methods disclosed herein provide methods to examine the expression level of one or more of these marker genes in a lymphoma sample (e.g., B-cell lymphoma sample). In some embodiments, the expression level relative a reference level is examined for one or more marker genes. The methods and assays include those which examine expression of marker genes such as one or more of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B. Expression levels may be measured at mRNA level and/or protein level.

[0087] The invention provides methods for measuring levels of expression from a mammalian tissue or cells sample (such as cells and/or tissues associated with B-cell lymphoma). For example, for obtaining patient samples, H&E staining is carried out and used as a guide for tissue macrodissection to enrich for tumor content. The sample can be obtained by a variety of procedures known in the art including, but is not limited to surgical excision, aspiration or biopsy. The sample may be fresh or frozen. In some embodiments, the sample is fixed and embedded in paraffin or the like. In the methods, a mammalian tissue or cell sample is obtained and examined for expression of one or more biomarkers. The methods may be conducted in a variety of assay formats, including assays detecting mRNA expression, enzymatic assays detecting presence of enzymatic activity, and immunohistochemistry assays. Determination of expression of such biomarkers in said tissues or cells will be predictive that such tissues or cells will be sensitive/responsive to treatment with an anti-CD40 antibody.

[0088] As discussed below, expression of various biomarkers in a sample can be analyzed by a number of methodologies, many of which are known in the art and understood by the skilled artisan, including but are not limited to, microarray (gene and/or tissue array analysis), *in situ* hybridization, Northern analysis, PCR analysis of mRNAs, immunohistochemical and/or Western analysis, FACS, protein arrays, mass spectrometry, quantitative blood based assays (as for example Serum ELISA) (to examine, for example, levels of protein expression), and/or biochemical enzymatic activity assays. Typical protocols for evaluating the status of genes and gene products are found, for example in Ausubel et al. eds., 1995, Current Protocols In Molecular Biology, Units 2 (Northern Blotting), 4 (Southern Blotting), 15 (Immunoblotting) and 18 (PCR Analysis). The protocols below relating to detection of particular biomarkers, such as expression level of one or more of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B, in a sample are provided for illustrative purposes.

[0089] In some embodiments, the methods of the invention further include protocols which examine the presence and/or expression of mRNAs, such as mRNAs of at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, at least fourteen, or fifteen genes from UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B, in a tissue or cell sample. In some embodiments, expression of various biomarkers in a sample may be analyzed by microarray technologies, which examine or detect mRNAs, in a tissue or cell sample. Using nucleic acid microarrays,

test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. For example, a selection of genes that have potential to be expressed in certain disease states may be arrayed on a solid support.

Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene. Differential gene expression analysis of disease tissue can provide valuable information. Microarray technology utilizes nucleic acid hybridization techniques and computing technology to evaluate the mRNA expression profile of thousands of genes within a single experiment. (See, e.g., WO 01/75166 published October 11, 2001; see also, for example, U.S. 5,700,637, U.S. Patent 5,445,934, and U.S. Patent 5,807,522, Lockart, *Nature Biotechnology*, 14:1675-1680 (1996); Cheung, V.G. et al., *Nature Genetics* 21(Suppl):15-19 (1999) for a discussion of array fabrication). DNA microarrays are miniature arrays containing gene fragments that are either synthesized directly onto or spotted onto glass or other substrates. Thousands of genes are usually represented in a single array. A typical microarray experiment involves the following steps: 1) preparation of fluorescently labeled target from RNA isolated from the sample, 2) hybridization of the labeled target to the microarray, 3) washing, staining, and scanning of the array, 4) analysis of the scanned image and 5) generation of gene expression profiles. Currently two main types of DNA microarrays are being used: oligonucleotide (usually 25 to 70 mers) arrays and gene expression arrays containing PCR products prepared from cDNAs. In forming an array, oligonucleotides can be either prefabricated and spotted to the surface or directly synthesized on to the surface (in situ).

[0090] The Affymetrix GeneChip® system is a commercially available microarray system which comprises arrays fabricated by direct synthesis of oligonucleotides on a glass surface. Probe/Gene Arrays: Oligonucleotides, usually 25 mers, are directly synthesized onto a glass wafer by a combination of semiconductor-based photolithography and solid phase chemical synthesis technologies. Each array contains up to 400,000 different oligos and each oligo is present in millions of copies. Since oligonucleotide probes are synthesized in known locations on the array, the hybridization patterns and signal intensities can be interpreted in terms of gene identity and relative expression levels by the Affymetrix Microarray Suite software. Each gene is represented on the array by a series of different oligonucleotide probes. Each probe pair consists of a perfect match oligonucleotide and a mismatch oligonucleotide. The perfect match probe has a sequence exactly complementary to the

particular gene and thus measures the expression of the gene. The mismatch probe differs from the perfect match probe by a single base substitution at the center base position, disturbing the binding of the target gene transcript. This helps to determine the background and nonspecific hybridization that contributes to the signal measured for the perfect match oligo. The Microarray Suite software subtracts the hybridization intensities of the mismatch probes from those of the perfect match probes to determine the absolute or specific intensity value for each probe set. Probes are chosen based on current information from GenBank and other nucleotide repositories. The sequences are believed to recognize unique regions of the 3' end of the gene. A GeneChip Hybridization Oven ("rotisserie" oven) is used to carry out the hybridization of up to 64 arrays at one time. The fluidics station performs washing and staining of the probe arrays. It is completely automated and contains four modules, with each module holding one probe array. Each module is controlled independently through Microarray Suite software using preprogrammed fluidics protocols. The scanner is a confocal laser fluorescence scanner which measures fluorescence intensity emitted by the labeled cRNA bound to the probe arrays. The computer workstation with Microarray Suite software controls the fluidics station and the scanner. Microarray Suite software can control up to eight fluidics stations using preprogrammed hybridization, wash, and stain protocols for the probe array. The software also acquires and converts hybridization intensity data into a presence/absence call for each gene using appropriate algorithms. Finally, the software detects changes in gene expression between experiments by comparison analysis and formats the output into .txt files, which can be used with other software programs for further data analysis.

[0091] In some embodiments, expression of various biomarkers in a sample may also be assessed by examining gene deletion or gene amplification. Gene deletion or amplification may be measured by any one of a wide variety of protocols known in the art, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA (Thomas, *Proc. Natl. Acad. Sci. USA*, 77:5201-5205 (1980)), dot blotting (DNA analysis), or *in situ* hybridization (e.g., FISH), using an appropriately labeled probe, cytogenetic methods or comparative genomic hybridization (CGH) using an appropriately labeled probe. By way of example, these methods may be employed to detect deletion or amplification of genes.

[0092] In some embodiments, expression of various biomarkers in a sample may be assessed by hybridization assays using complementary DNA probes (such as *in situ* hybridization using labeled riboprobes, Northern blot and related techniques) and various nucleic acid amplification assays (such as RT-PCR using complementary primers, such as

primers specific for one or more genes of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B, and other amplification type detection methods, such as, branched DNA, SISBA, TMA and the like).

[0093] Tissue or cell samples from mammals can be conveniently assayed for, *e.g.*, mRNAs of any one or more of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B genes, using Northern, dot blot or PCR analysis. In some embodiments, expression of one or more biomarkers may be assayed by RT-PCR. In some embodiments, RT-PCR is quantitative RT-PCR (qRT-PCR). In some embodiments, RT-PCR is real-time RT-PCR. In some embodiments, RT-PCR is quantitative real-time RT-PCR. RT-PCR assays such as quantitative PCR assays are well known in the art. In an illustrative embodiment of the invention, a method for detecting a mRNA in a biological sample comprises producing cDNA from the sample by reverse transcription using at least one primer; amplifying the cDNA so produced using a polynucleotide as sense and antisense primers to amplify cDNAs therein; and detecting the presence of the amplified cDNA of interest. In some embodiments, real-time RT-PCR is quantitative RT-PCR. In some embodiments, real-time RT-PCR may be performed using TaqMan® chemistry (Applied Biosystems). In some embodiments, real-time RT-PCR may be performed using TaqMan® chemistry (Applied Biosystems) and the ABI Prism® 7700 Sequence Detection System (Applied Biosystems). Real-time RT-PCR combines the principles that Taq polymerase has a 5'-3' exonuclease activity and dual-labeled fluorogenic oligonucleotide problems have been created which emit a fluorescent signal only upon cleavage, based on the principle of fluorescence resonance energy transfer. *See, e.g., Overbergh, L. et al., J. Biomolecular Techniques* 14(1): 33-43 (2003). In addition, such methods can include one or more steps that allow one to determine the levels of mRNA, in a biological sample (*e.g.*, by simultaneously examining the levels a comparative control mRNA sequence of a "housekeeping" gene such as an actin family member and/or one or more genes listed in Tables 8 and 9 in WO 2009/062125). Examples of primers and probes that may be used for conducting qRT-PCR are provided in Table 1.

[0094] In some embodiments, the expression of proteins encoded by UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B in a sample is examined using immunohistochemistry and staining protocols. Immunohistochemical staining of tissue sections has been shown to be a reliable method of assessing or detecting presence of proteins in a sample. Immunohistochemistry ("IHC")

techniques utilize an antibody to probe and visualize cellular antigens *in situ*, generally by chromogenic or fluorescent methods.

[0095] For sample preparation, a tissue or cell sample from a mammal (typically a human patient) may be used. Examples of samples include, but are not limited to, tissue biopsy, blood, lung aspirate, sputum, lymph fluid, etc. The sample can be obtained by a variety of procedures known in the art including, but not limited to surgical excision, aspiration or biopsy. The tissue may be fresh or frozen. In some embodiments, the sample is fixed and embedded in paraffin or the like.

[0096] The tissue sample may be fixed (*i.e.* preserved) by conventional methodology (See *e.g.*, “Manual of Histological Staining Method of the Armed Forces Institute of Pathology,” 3rd edition (1960) Lee G. Luna, HT (ASCP) Editor, The Blakston Division McGraw-Hill Book Company, New York; *The Armed Forces Institute of Pathology Advanced Laboratory Methods in Histology and Pathology* (1994) Ulreka V. Mikel, Editor, Armed Forces Institute of Pathology, American Registry of Pathology, Washington, D.C.). One of skill in the art will appreciate that the choice of a fixative is determined by the purpose for which the sample is to be histologically stained or otherwise analyzed. One of skill in the art will also appreciate that the length of fixation depends upon the size of the tissue sample and the fixative used. By way of example, neutral buffered formalin, Bouin’s or paraformaldehyde, may be used to fix a sample.

[0097] Generally, the sample is first fixed and is then dehydrated through an ascending series of alcohols, infiltrated and embedded with paraffin or other sectioning media so that the tissue sample may be sectioned. Alternatively, one may section the tissue and fix the sections obtained. By way of example, the tissue sample may be embedded and processed in paraffin by conventional methodology (See *e.g.*, “Manual of Histological Staining Method of the Armed Forces Institute of Pathology”, *supra*). Examples of paraffin that may be used include, but are not limited to, Paraplast, Broloid, and Tissuemay. Once the tissue sample is embedded, the sample may be sectioned by a microtome or the like (See *e.g.*, “Manual of Histological Staining Method of the Armed Forces Institute of Pathology”, *supra*). By way of example for this procedure, sections may range from about three microns to about five microns in thickness. Once sectioned, the sections may be attached to slides by several standard methods. Examples of slide adhesives include, but are not limited to, silane, gelatin, poly-L-lysine and the like. By way of example, the paraffin embedded sections may be attached to positively charged slides and/or slides coated with poly-L-lysine.

[0098] If paraffin has been used as the embedding material, the tissue sections are generally deparaffinized and rehydrated to water. The tissue sections may be deparaffinized by several conventional standard methodologies. For example, xylenes and a gradually descending series of alcohols may be used (*See e.g.*, “Manual of Histological Staining Method of the Armed Forces Institute of Pathology”, *supra*). Alternatively, commercially available deparaffinizing non-organic agents such as Hemo-De7 (CMS, Houston, Texas) may be used.

[0099] In some embodiments, subsequent to the sample preparation, a tissue section may be analyzed using IHC. IHC may be performed in combination with additional techniques such as morphological staining and/or fluorescence *in-situ* hybridization. Two general methods of IHC are available; direct and indirect assays. According to the first assay, binding of antibody to the target antigen (*e.g.*, a protein or fragment thereof encoded by any of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B) is determined directly. This direct assay uses a labeled reagent, such as a fluorescent tag or an enzyme-labeled primary antibody, which can be visualized without further antibody interaction. In a typical indirect assay, unconjugated primary antibody binds to the antigen and then a labeled secondary antibody binds to the primary antibody. Where the secondary antibody is conjugated to an enzymatic label, a chromogenic or fluorogenic substrate is added to provide visualization of the antigen. Signal amplification occurs because several secondary antibodies may react with different epitopes on the primary antibody.

[0100] The primary and/or secondary antibody used for immunohistochemistry typically will be labeled with a detectable moiety. Numerous labels are available which can be generally grouped into the following categories:

(a) Radioisotopes, such as ^{35}S , ^{14}C , ^{125}I , ^3H , and ^{131}I . The antibody can be labeled with the radioisotope using the techniques described in *Current Protocols in Immunology*, Volumes 1 and 2, Coligen *et al.*, Ed. Wiley-Interscience, New York, New York, Pubs. (1991) for example and radioactivity can be measured using scintillation counting.

(b) Colloidal gold particles.

(c) Fluorescent labels including, but are not limited to, rare earth chelates (europium chelates), Texas Red, rhodamine, fluorescein, dansyl, Lissamine, umbelliferone, phycocrytherin, phycocyanin, or commercially available fluorophores such SPECTRUM ORANGE7 and SPECTRUM GREEN7 and/or derivatives of any one or more of the above. The fluorescent labels can be conjugated to the antibody using the techniques disclosed in *Current Protocols in Immunology*, *supra*, for example. Fluorescence can be quantified using a fluorimeter.

(d) Various enzyme-substrate labels are available and U.S. Patent No. 4,275,149 provides a review of some of these. The enzyme generally catalyzes a chemical alteration of the chromogenic substrate that can be measured using various techniques. For example, the enzyme may catalyze a color change in a substrate, which can be measured spectrophotometrically. Alternatively, the enzyme may alter the fluorescence or chemiluminescence of the substrate. Techniques for quantifying a change in fluorescence are described above. The chemiluminescent substrate becomes electronically excited by a chemical reaction and may then emit light which can be measured (using a chemiluminometer, for example) or donates energy to a fluorescent acceptor. Examples of enzymatic labels include luciferases (*e.g.*, firefly luciferase and bacterial luciferase; U.S. Patent No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, malate dehydrogenase, urease, peroxidase such as horseradish peroxidase (HRPO), alkaline phosphatase, β -galactosidase, glucoamylase, lysozyme, saccharide oxidases (*e.g.*, glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase), heterocyclic oxidases (such as uricase and xanthine oxidase), lactoperoxidase, microperoxidase, and the like. Techniques for conjugating enzymes to antibodies are described in O'Sullivan *et al.*, Methods for the Preparation of Enzyme-Antibody Conjugates for use in Enzyme Immunoassay, in *Methods in Enzym.* (ed. J. Langone & H. Van Vunakis), Academic press, New York, 73:147-166 (1981).

[0101] Examples of enzyme-substrate combinations include, for example:

- (i) Horseradish peroxidase (HRPO) with hydrogen peroxide as a substrate, wherein the hydrogen peroxidase oxidizes a dye precursor (*e.g.*, orthophenylene diamine (OPD) or 3,3',5,5'-tetramethyl benzidine hydrochloride (TMB));
- (ii) alkaline phosphatase (AP) with para-Nitrophenyl phosphate as chromogenic substrate; and
- (iii) β -D-galactosidase (β -D-Gal) with a chromogenic substrate (*e.g.*, p-nitrophenyl- β -D-galactosidase) or fluorogenic substrate (*e.g.*, 4-methylumbelliferyl- β -D-galactosidase).

[0102] Numerous other enzyme-substrate combinations are available to those skilled in the art. For a general review of these, see U.S. Patent Nos. 4,275,149 and 4,318,980. Sometimes, the label is indirectly conjugated with the antibody. The skilled artisan will be aware of various techniques for achieving this. For example, the antibody can be conjugated with biotin and any of the four broad categories of labels mentioned above can be conjugated with avidin, or *vice versa*. Biotin binds selectively to avidin and thus, the label can be conjugated

with the antibody in this indirect manner. Alternatively, to achieve indirect conjugation of the label with the antibody, the antibody is conjugated with a small hapten and one of the different types of labels mentioned above is conjugated with an anti-hapten antibody. Thus, indirect conjugation of the label with the antibody can be achieved.

[0103] Aside from the sample preparation procedures discussed above, further treatment of the tissue section prior to, during or following IHC may be desired. For example, epitope retrieval methods, such as heating the tissue sample in citrate buffer may be carried out (*see, e.g., Leong et al. Appl. Immunohistochem.* 4(3):201 (1996)).

[0104] Following an optional blocking step, the tissue section is exposed to primary antibody for a sufficient period of time and under suitable conditions such that the primary antibody binds to the target protein antigen in the tissue sample. Appropriate conditions for achieving this can be determined by routine experimentation. The extent of binding of antibody to the sample is determined by using any one of the detectable labels discussed above. Preferably, the label is an enzymatic label (*e.g.* HRPO) which catalyzes a chemical alteration of the chromogenic substrate such as 3,3'-diaminobenzidine chromogen. Preferably the enzymatic label is conjugated to antibody which binds specifically to the primary antibody (*e.g.* the primary antibody is rabbit polyclonal antibody and secondary antibody is goat anti-rabbit antibody).

[0105] In some embodiments, the antibodies employed in the IHC analysis to detect expression of one or more biomarkers are antibodies generated to bind primarily to the one or more biomarkers of interest, such as one or more proteins encoded by UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B. In some embodiments, the antibody is a monoclonal antibody. Antibodies are readily available in the art, including from various commercial sources, and can also be generated using routine skills known in the art.

[0106] Specimens thus prepared may be mounted and coverslipped. Slide evaluation is then determined, *e.g.* using a microscope, and staining intensity criteria, routinely used in the art, may be employed. As one example, staining intensity criteria may be evaluated as follows:

Table A

Staining Pattern	Score
No staining is observed in cells.	0
Faint/barely perceptible staining is detected in more than 10% of the cells.	1+

Weak to moderate staining is observed in more than 10% of the cells.	2+
Moderate to strong staining is observed in more than 10% of the cells.	3+

[0107] In alternative methods, the sample may be contacted with an antibody specific for said biomarker under conditions sufficient for an antibody-biomarker complex to form, and then detecting said complex. The presence of the biomarker may be detected in a number of ways, such as by Western blotting and ELISA procedures for assaying a wide variety of tissues and samples, including plasma or serum. A wide range of immunoassay techniques using such an assay format are available, *see, e.g.*, U.S. Pat. Nos. 4,016,043, 4,424,279 and 4,018,653. These include both single-site and two-site or "sandwich" assays of the non-competitive types, as well as in the traditional competitive binding assays. These assays also include direct binding of a labeled antibody to a target biomarker.

[0108] Sandwich assays are among the most useful and commonly used assays. A number of variations of the sandwich assay technique exist, and all are intended to be encompassed by the present invention. Briefly, in a typical forward assay, an unlabelled antibody is immobilized on a solid substrate, and the sample to be tested brought into contact with the bound molecule. After a suitable period of incubation, for a period of time sufficient to allow formation of an antibody-antigen complex, a second antibody specific to the antigen, labeled with a reporter molecule capable of producing a detectable signal is then added and incubated, allowing time sufficient for the formation of another complex of antibody-antigen-labeled antibody. Any unreacted material is washed away, and the presence of the antigen is determined by observation of a signal produced by the reporter molecule. The results may either be qualitative, by simple observation of the visible signal, or may be quantitated by comparing with a control sample containing known amounts of biomarker.

[0109] Variations on the forward assay include a simultaneous assay, in which both sample and labeled antibody are added simultaneously to the bound antibody. These techniques are well known to those skilled in the art, including any minor variations as will be readily apparent. In a typical forward sandwich assay, a first antibody having specificity for the biomarker is either covalently or passively bound to a solid surface. The solid surface is typically glass or a polymer, the most commonly used polymers being cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene. The solid supports may be in the form of tubes, beads, discs of microplates, or any other surface suitable for

conducting an immunoassay. The binding processes are well-known in the art and generally consist of cross-linking covalently binding or physically adsorbing, the polymer-antibody complex is washed in preparation for the test sample. An aliquot of the sample to be tested is then added to the solid phase complex and incubated for a period of time sufficient (*e.g.*, 2-40 minutes or overnight if more convenient) and under suitable conditions (*e.g.*, from room temperature to 40°C such as between 25° C and 32° C inclusive) to allow binding of any subunit present in the antibody. Following the incubation period, the antibody subunit solid phase is washed and dried and incubated with a second antibody specific for a portion of the biomarker. The second antibody is linked to a reporter molecule which is used to indicate the binding of the second antibody to the molecular marker.

[0110] In some embodiments, the methods involves immobilizing the target biomarkers in the sample and then exposing the immobilized target to specific antibody which may or may not be labeled with a reporter molecule. Depending on the amount of target and the strength of the reporter molecule signal, a bound target may be detectable by direct labeling with the antibody. Alternatively, a second labeled antibody, specific to the first antibody is exposed to the target-first antibody complex to form a target-first antibody-second antibody tertiary complex. The complex is detected by the signal emitted by the reporter molecule. By "reporter molecule", as used in the present specification, is meant a molecule which, by its chemical nature, provides an analytically identifiable signal which allows the detection of antigen-bound antibody. The most commonly used reporter molecules in this type of assay are either enzymes, fluorophores or radionuclide containing molecules (*i.e.* radioisotopes) and chemiluminescent molecules.

[0111] In the case of an enzyme immunoassay, an enzyme is conjugated to the second antibody, generally by means of glutaraldehyde or periodate. As will be readily recognized, however, a wide variety of different conjugation techniques exist, which are readily available to the skilled artisan. Commonly used enzymes include horseradish peroxidase, glucose oxidase, -galactosidase and alkaline phosphatase, amongst others. The substrates to be used with the specific enzymes are generally chosen for the production, upon hydrolysis by the corresponding enzyme, of a detectable color change. Examples of suitable enzymes include alkaline phosphatase and peroxidase. It is also possible to employ fluorogenic substrates, which yield a fluorescent product rather than the chromogenic substrates noted above. In all cases, the enzyme-labeled antibody is added to the first antibody-molecular marker complex, allowed to bind, and then the excess reagent is washed away. A solution containing the appropriate substrate is then added to the complex of antibody-antigen-antibody. The

substrate will react with the enzyme linked to the second antibody, giving a qualitative visual signal, which may be further quantitated, usually spectrophotometrically, to give an indication of the amount of biomarker which was present in the sample. Alternately, fluorescent compounds, such as fluorescein and rhodamine, may be chemically coupled to antibodies without altering their binding capacity. When activated by illumination with light of a particular wavelength, the fluorochrome-labeled antibody adsorbs the light energy, inducing a state to excitability in the molecule, followed by emission of the light at a characteristic color visually detectable with a light microscope. As in the EIA, the fluorescent labeled antibody is allowed to bind to the first antibody-molecular marker complex. After washing off the unbound reagent, the remaining tertiary complex is then exposed to the light of the appropriate wavelength, the fluorescence observed indicates the presence of the molecular marker of interest. Immunofluorescence and EIA techniques are both very well established in the art. However, other reporter molecules, such as radioisotope, chemiluminescent or bioluminescent molecules, may also be employed.

[0112] In some embodiments, expression of a selected biomarker in a tissue or cell sample may be examined by way of functional or activity-based assays. For instance, if the biomarker is an enzyme, one may conduct assays known in the art to determine or detect the presence of the given enzymatic activity in the tissue or cell sample.

[0113] In any of the above methods of assessing level of expression of one or more biomarkers, a sample comprising a target molecule can be obtained by methods well known in the art, and that are appropriate for the particular type and location of the disease of interest. Tissue biopsy is often used to obtain a representative piece of disease tissue. Alternatively, cells can be obtained indirectly in the form of tissues/fluids that are known or thought to contain the disease cells of interest. For instance, samples of disease lesions may be obtained by resection, bronchoscopy, fine needle aspiration, bronchial brushings, or from sputum, pleural fluid or blood. Genes or gene products can be detected from disease tissue or from other body samples such as urine, sputum or serum. The same techniques discussed above for detection of target genes or gene products in disease samples can be applied to other body samples. By screening such body samples, a simple early diagnosis can be achieved for these diseases. In addition, the progress of therapy can be monitored more easily by testing such body samples for target genes or gene products.

[0114] Means for enriching a tissue preparation for disease cells are known in the art. For example, the tissue may be isolated from paraffin or cryostat sections. Cells of interest may also be separated from normal cells by flow cytometry or laser capture microdissection.

These, as well as other techniques for separating disease from normal cells, are well known in the art. If the disease tissue is highly contaminated with normal cells, detection of signature gene expression profile may be more difficult, although techniques for minimizing contamination and/or false positive/negative results are known, some of which are described herein below. For example, a sample may also be assessed for the presence of a biomarker (including a mutation) known to be associated with a disease cell of interest but not a corresponding normal cell, or vice versa.

[0115] Subsequent to the determination that the tissue or cell sample expresses one or more of the biomarkers indicating the tissue or cell sample will be sensitive to treatment with anti-CD40 antibodies, it is contemplated that an effective amount of the anti-CD40 antibody may be administered to the mammal, such as a human to treat a disorder, such as a B-cell lymphoma which is afflicting the mammal. Diagnosis in mammals, such as humans, of the various pathological conditions described herein can be made by the skilled practitioner.

Comparing expression levels and predicting, assessing or aiding assessment of responsiveness of B-cell lymphoma to an anti-CD40 antibody treatment

[0116] The methods described herein comprise a process of comparing a measured expression level of a marker gene and a reference level. The reference level may be a measured expression level of a reference gene different from the marker gene or a measured expression level of the same marker gene in a different sample.

[0117] In some embodiments, a measured expression level of a marker gene in a B cell lymphoma sample from a subject is compared to a measured expression level of a reference gene in the sample. In some embodiments, the expression level of the reference gene does not substantially change among various types of B lymphoma cells, including anti-CD40 antibody sensitive and resistant cells. In some embodiments, the ratio of the measured expression level of the marker gene to the measured expression level of the reference is calculated, and the ratio may be used for assessing or aiding assessment of responsiveness of the B cell lymphoma to an anti-CD antibody treatment.

[0118] In some embodiments, a measured expression level of a marker gene in a B cell lymphoma sample from a subject is compared to a measured expression level of the marker gene in a reference sample. In some embodiments, the reference sample comprises B lymphoma cells that are resistant or not responsive to an anti-CD40 antibody. For example, the comparison is performed to determine the magnitude of the difference between the measured expression levels of the marker gene in the sample from the subject and in the

reference sample (*e.g.*, comparing the fold or percentage difference between the expression levels of the marker gene in the sample from the subject and the reference sample). In some embodiments, an increase or decreased expression of a marker gene in the sample from the subject as compared to the expression of the marker gene in the reference sample comprising B lymphoma cells that are resistant or not responsive to an anti-CD40 antibody suggests or indicates responsiveness of the B-cell lymphoma to treatment with an anti-CD40 antibody. In some embodiments, a fold of increase in the expression level of the sample from the subject can be at least about any of 1.5X, 1.75X, 2X, 3X, 4X, 5X, 6X, 7X, 8X, 9X, or 10X the expression level of the reference sample. In some embodiments, a fold of decrease in the expression level of the sample from the subject can be less than about any of 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 of the expression level of the reference sample.

[0119] In some embodiments, the expression levels of one or more marker genes selected from the group consisting of IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7 are compared to a reference level.

[0120] In some embodiments, an increased expression level of one or more of IFITM1, CD79B, IGF1R, CD44, CTSC, EPDR1, and PUS7 as compared to a reference level indicates that said subject is less likely to respond to an agonist anti-CD40 antibody treatment. In some embodiments, the reference level is a value or a range determined by expression levels of the corresponding marker gene in samples comprising B lymphoma cells from subjects having tumor volume increased after an agonist anti-CD40 antibody treatment.

[0121] In some embodiments, an increased expression of one or more of CD40, RGS13, VNN2, LMO2, CD22, BTG2, and UAP1 as compared to a reference level indicates that said subject is likely to respond to the agonist anti-CD40 antibody treatment. In some embodiments, the reference level is a value or a range determined by expression levels of the corresponding marker gene in samples comprising B lymphoma cells from subjects having tumor volume decreased after an agonist anti-CD40 antibody treatment.

[0122] In some embodiments, the expression level BCL6 is measured and compared to a reference level. The expression level of BCL6 is used for predicting, assessing, or aiding assessment of responsiveness of the subject to an anti-CD40 antibody treatment. As shown in Example 1, BCL6 expression trends lower in those subjects with tumor increases after an agonist anti-CD40 antibody treatment. In some embodiments, an increased expression of BCL6 as compared to a reference level determined by expression level of BCL6 in samples from subjects having tumor volume decreased after an agonist anti-CD40 antibody treatment may indicate the subject is likely to respond to the agonist anti-CD40 antibody treatment.

[0123] In some embodiments, the expression levels of one or more of IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, PUS7, and BCL6 are measured, and a sensitivity index is calculated based on the measured expression level of the marker genes. For example, the following equation may be used for determining sensitivity index (SI):

$$SI = \sum_{j=1}^p \beta_j \frac{x_j - \hat{\mu}_j}{\sqrt{\hat{\sigma}_j^2}}$$

wherein expression level of at least one marker gene having a positive correlation value and at least one marker gene having a negative correlation value shown in Table 4 are measured; wherein (i) β_j is the coefficient value for each marker genes measured; (ii) p is the number of marker genes measured; (iii) x_j is transformed, normalized expression level for the sample from the subject for expression level of each marker measured; and (iv) μ_j and σ_j are means and standard deviations for each marker gene measured; wherein β_j , μ_j and σ_j are determined from patient samples comprising B lymphoma cells from a clinical trial. In some embodiments, a value equals or greater than zero for the sensitivity index indicates that the subject is likely to respond the anti-CD40 antibody treatment, or wherein a value less than zero for the sensitivity index indicates that the subject is less likely to respond the anti-CD40 antibody treatment. Examples 1 described in detail how to analyze and determine parameters for reference samples and new samples. In some embodiments, the expression levels of IFITM1, RGS13, CD79B, CD22, BTG2, CD44, EPDR1, and UAP1 are measured and used for the sensitivity index calculation. In some embodiments, equal number of positive correlated marker genes and negative correlated marker genes are measured and used for the sensitivity index calculation.

[0124] Methods for determining sensitivity index are known in the art. See Zhou H. and Hastie T. (2005) *Regularization and variable selection via the elastic net*; J. R. Statist. Soc. B. 67(2). pp. 301-320; Friedman J., Hastie T. and Tibshirani R. 2008. *Regularization Paths for Generalized Linear Models via Coordinate Descent*. Technical Report, Department of Statistics, Stanford University (World Wide Web-
stat.stanford.edu/~hastie/Papers/glmnet.pdf) R package glmnet; R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL World Wide Web at R-project.org.

[0125] An alternative method using weighted K-nearest neighbors (WKNN) to classify a patient sample as responsive to an anti-CD40 antibody treatment is described in Example 2. The qRT-PCR is used to measure expression of 15 genes, UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B. Tumor size reduction of at least 10% is defined as being responsive to the anti-CD40 antibody treatment. Weights for the 15 genes are determined using penalized regression (GLMNET).

[0126] In some embodiments, the methods of the invention comprise classifying the subject as a responsive or non-responsive subject using a K-nearest neighbors analysis based on the expression level of said one or more marker genes of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B in the sample from the subject and reference samples with known classes. In some embodiments, classifying the subject using a K-nearest neighbors analysis is carried out by (1) determining parameter K (i.e., number of nearest neighbors); (2) calculating the difference between the measured expression level of the marker genes in the new sample to be classified and the expression level of the respective marker genes in each reference sample; (3) determining the nearest reference samples by selecting those samples with the smallest weighted average of the absolute differences (WAAD) between the new sample and the reference sample; and (4) determining class of the new sample based on the known classes of the K nearest reference samples. The weights and/or parameter K are determined using cross-validation with clinical trial samples with known classes. For example, 5-fold (such as 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, or 10-fold) to N-fold cross-validation may be used to minimize the weighted K-nearest neighbors classification error, wherein N is the size of the samples. In some embodiments, K is an integer between 4 and 13 (e.g., 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13). In some embodiments, the nearest reference samples (nearest neighbors) are those with the smallest weighted average of the absolute differences (WADD) between the expression level of the new sample to be classified and the expression level of each reference sample for each of the 15 marker genes UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B. In some embodiments, the weights for the WAAD are the absolute values of the coefficients from an elastic net penalized regression of reference sample tumor shrinkage on the expression levels of the 15 marker genes. In some embodiments, the magnitude of the penalty is chosen by 10 fold cross-validation to minimize the WKNN classification error. Weights for the 15 genes may be determined using penalized regression (GLMNET). In some embodiments, qRT-PCR is used to measure expression

levels of the 15 genes, UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B. In some embodiments, the K nearest reference samples contribute to the inverse of their WADD (i.e., 1 divided by the WAAD) in the manner of a vote for their known class label, and the class label with the largest total inverse WAAD contributions is assigned to the new sample. In some embodiments, a patient is considered as being responsive to an anti-CD40 antibody treatment if the patient has at least 10% tumor size reduction after the anti-CD40 antibody treatment. Tumor size reduction may be determined by the sum of the product of diameters (SPD). Example 2 provides a detailed description of using the weighted K-nearest neighbors method with 39 DLBCL patient samples as reference samples.

[0127] The comparisons and/or calculations for predicting, assessing or aiding assessment can be carried out in any convenient manner appropriate to the type of measured value and/or reference value for the gene markers at issue. The process of comparing or calculating may be manual or it may be automatic (such as by a machine including computer-based machine). In some embodiments, measured expression levels are normalized values. For example, the expression level may be normalized based on the equation under Transformed, Normalized Assay Values described in Example 1. As will be apparent to those of skill in the art, replicate measurements may be taken for the expression levels of marker genes and/or reference genes. In some embodiments, replicate measurements are taking into account for the measured values. The replicate measurements may be taken into account by using either the mean or median of the measured values as the “measured value”. Statistical analysis known in the art may be used to verify the significance of the difference between the two values compared.

Anti-CD40 Antibody Treatment

[0128] The marker genes identified in the invention may be used for predicting, assessing, or aiding assessment of responsiveness of B-cell lymphoma to treatment with one or more anti-CD40 antibodies. The anti-CD40 antibodies may be one or more agonist antibodies (i.e., bind and stimulate CD40). Stimulatory antibodies can be of different types, such as: (1) those that deliver a stimulatory signal through CD40 but do not increase the interaction between CD40 and CD40L (e.g., antibody G28-5 and antibodies derived from G28-5 described in U.S. Pat. No. 5,182,368; and PCT WO 96/18413), or decrease the interaction between CD40 and CD40L (e.g., antibodies HuCD40-M2 and HuCD40-M3 and humanized antibodies described in U.S. Pat. No. 5,674,492; and (2) those that deliver a stimulatory

signal through CD40 and can increase the interaction between CD40 and CD40L, e.g., S2C6 (Francisco et al., 2000, *Cancer Res.* 60:3225-31) and antibodies derived from S2C6.

Agonists antibodies are also described in U.S. Pat. No. 7,288,251. The anti-CD40 antibodies may be one or more antagonist antibodies (i.e., bind CD40 and inhibit activities induced by CD40L). Examples of antagonist anti-CD40 antibodies include human antibody CHIR-12.12 described in U.S. Pub. No. 2007/0110754, and anti-CD40 antibodies described in WO 97/31025. In some embodiments, the anti-CD40 antibody comprises the heavy chain amino acid sequence of SEQ ID NO:1 and the light chain amino acid sequence of SEQ ID NO:2.

[0129] The methods of the invention may further comprise administering an effective amount of an anti-CD40 antibody to a subject having a B-cell lymphoma after the subject has been identified as a candidate for treatment based on the assays/methods described herein. One or more anti-CD40 antibodies may be administered. In some embodiments, the anti-CD40 antibody is administered in conjunction with one or more other therapeutic agents. For example, the anti-CD40 antibody is administered in conjunction with one or more of the following therapeutic agents: rituximab, gemzar, and ICE. For example, an anti-CD40 antibody can be administered to the patient in conjunction with rituximab therapy; with rituximab plus gemzar; with rituximab plus ICE (ifosfamide, carboplatin, etoposide) (R-ICE); or with rituximab plus chemotherapy.

[0130] As used herein, administration "in conjunction" includes simultaneous administration and/or administration at different times. Administration in conjunction also encompasses administration as a co-formulation (i.e., different drugs are present in the same composition) or administration as separate compositions, administration at different dosing frequencies or intervals, and administration using the same route or different routes.

[0131] The anti-CD40 antibodies or functional fragments can be used for the treatment of patients with NHL that are nonresponsive or have an inadequate response to treatment with any one of the following drugs: rituximab (Genentech); ocrelizumab (Genentech, Inc.); ibritumomab tiuxetan (Zevalin™, Biogen Idec); tositumomab (Bexxar™, GlaxoSmithKline); HuMAX-CD20™ (GenMab); IMMU-106 (which is a humanized anti-CD20 a.k.a. hA20 or 90Y-hLL2, Immunomedics); AME-133 (Applied Molecular Evolution/Eli Lilly); gentuzumab ozogamicin (Mylotarg™, a humanized anti-CD33 antibody, Wyeth/PDL); alemtuzumab (Campath™, an anti-CD52 antibody, Schering Plough/Genzyme); epratuzumab (IMMU-103™, a humanized anti-CD22 antibody, Immunomedics), or have relapsed after treatment with these drugs.

[0132] The following references describe lymphomas and CLL, their diagnoses, treatment and standard medical procedures for measuring treatment efficacy. Canellos GP, Lister, TA, Sklar JL: *The Lymphomas*. W.B.Saunders Company, Philadelphia, 1998; van Besien K and Cabanillas, F: Clinical Manifestations, Staging and Treatment of Non-Hodgkin's Lymphoma, Chap. 70, pp 1293-1338, in: *Hematology, Basic Principles and Practice*, 3rd ed. Hoffman et al. (editors). Churchill Livingstone, Philadelphia, 2000; and Rai, K and Patel, D: Chronic Lymphocytic Leukemia, Chap. 72, pp 1350-1362, in: *Hematology, Basic Principles and Practice*, 3rd ed. Hoffman et al. (editors). Churchill Livingstone, Philadelphia, 2000.

[0133] Anti-CD40 antibodies for use in the treatment include chimeric, humanized and human antibodies. Any agonist or antagonist antibodies described herein or known in the art may be used in the treatment. For example, humanized anti-CD40 antibodies described in WO 2006/128103 may be used for the anti-CD40 antibody treatment, and these antibodies and their amino acid sequences are incorporated herein by reference. In some embodiments, the anti-CD40 antibody for use in the treatment described herein binds to CD40 (such as human CD40) expressed on B lymphoma cells and induces apoptosis of the B lymphoma cells. The anti-CD40 antibody may also have the characteristics of killing B lymphoma cells in vivo via immune effector functions, such as ADCC, CDC, and/or ADCP. In some embodiments, the anti-CD40 antibody binds to CD40 with a K_d value of no higher than about 1×10^{-8} or no higher than 1×10^{-9} . In some embodiments, the anti-CD40 antibody binds to CD40 and stimulates CD40 (i.e., an agonist antibody). In some embodiments, the anti-CD40 antibody increases the binding of CD40 ligand to CD40, for example, by at least 45%, by at least 50%, by at least 60%, or by at least 75%. A method of determining increases in binding of CD40 ligand to CD40 are disclosed in U.S. Pat. No. 6,838,261 (the disclosure of which is incorporated by reference herein). In some embodiments, the anti-CD40 is a humanized antibody derived from murine monoclonal antibody S2C6 described in WO 00/75348 (including antibodies provided in Tables 3 and 4 of WO 00/75348). In some embodiments, the anti-CD40 antibody comprises the heavy chain amino acid sequence shown in SEQ ID NO:1 and the light chain amino acid sequence shown in SEQ ID NO:2, for example anti-CD40 Ab.1.

D. Kits

[0134] For use in the applications described or suggested above, kits or articles of manufacture are also provided by the invention. Such kits may comprise at least one reagent

specific for detecting expression level of a marker gene described herein, and may further include instructions for carrying out a method described herein.

[0135] In some embodiments, the invention provides compositions and kits comprising primers and primer pairs, which allow the specific amplification of the polynucleotides of the invention or of any specific parts thereof, and probes that selectively or specifically hybridize to nucleic acid molecules of the invention or to any part thereof. Probes may be labeled with a detectable marker, such as, for example, a radioisotope, fluorescent compound, bioluminescent compound, a chemiluminescent compound, metal chelator or enzyme. Such probes and primers can be used to detect the presence of polynucleotides, such as the polynucleotides corresponding to genes UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B, in a sample and as a means for detecting cell expressing proteins encoded by the polynucleotides corresponding to genes UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B. As will be understood by the skilled artisan, a great many different primers and probes may be prepared based on the sequences provided herein and used effectively to amplify, clone and/or determine the presence and/or levels of mRNAs.

[0136] In some embodiments, the kits comprise reagents for detecting expression levels of at least two, at least three, at least five, at least ten, or fifteen marker genes selected from the group consisting of UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B. Kits may also comprise reference samples that are useful as generating reference values. The marker genes include, but are not limited to UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B. The reagents for detecting mRNA expression level of a marker gene may comprise at least one pair of primers specific for amplifying the mRNA products of one marker gene. In some embodiments, the pair of primers may target the 3' end of the mRNA sequence (*e.g.*, targeting mRNA at the 3' UTR which is usually shared in common with all transcript variants). In some embodiments, the kits may further comprise a surface or substrate (such as a microarray) for capture probes for detecting of amplified nucleic acids.

[0137] In some embodiments, the kits comprise at least one pair of primers and a probe specific for detecting one marker gene expression level using qRT-PCR. Examples of sets of primers and probes that can be used in qRT-PCR are shown in Table 1. For detecting IFITM1, primer and probe sets shown in SEQ ID NOS:27, 28 and 29, SEQ ID NOS:60, 61, and 62, and SEQ ID NOS:93, 94, and 95 may be used. For detecting CD40, primer and

probe sets shown in SEQ ID NOS:24, 25, and 26, SEQ ID NOS:57, 58, and 59, SEQ ID NOS:90, 91 and 92 may be used. For detecting RGS13, primer and probe sets shown in SEQ ID NOS:114, 115, and 116, and SEQ ID NOS:126, 127, and 128 may be used. For detecting VNN2, primer and probe sets shown in SEQ ID NOS:30, 31, and 32, SEQ ID NOS:63, 64, and 65, and SEQ ID NOS:96, 97, and 98. For detecting LMO2, primer and probe sets shown in SEQ ID NOS:12, 13, and 14, SEQ ID NOS:45, 46, and 47, and SEQ ID NOS:78, 79, and 80. For detecting CD79B, primer and probe sets shown in SEQ ID NOS:141, 142, and 143, SEQ ID NOS:150, 151, and 152, and SEQ ID NOS:159, 160, and 161. For detecting CD22, primer and probe sets shown in SEQ ID NOS:15, 16, and 17, SEQ ID NOS:48, 49, and 50, and SEQ ID NOS:81, 82, and 83. For detecting BTG2, primer and probe sets shown in SEQ ID NOS:9, 10, and 11, SEQ ID NOS:42, 43, and 44, and SEQ ID NOS:75, 76, and 77. For detecting IGF1R, primer and probe sets shown in SEQ ID NOS:6, 7, and 8, SEQ ID NOS:39, 40, and 41, and SEQ ID NOS:72, 73, and 74. For detecting CD44, primer and probe sets shown in SEQ ID NOS:174, 175, and 176, SEQ ID NOS:180, 181, and 182, and SEQ ID NOS:186, 187, and 188. For detecting CTSC, primer and probe sets shown in SEQ ID NOS:165, 166, and 167, SEQ ID NOS:168, 169, and 170, and SEQ ID NOS:171, 172, and 173. For detecting EPDR1, primer and probe sets shown in SEQ ID NOS:21, 22, and 23, SEQ ID NOS:54, 55, and 56, SEQ ID NOS:87, 88, and 89, SEQ ID NOS:129, 130, and 131, SEQ ID NOS:132, 133, and 134, SEQ ID NOS:135, 136, and 137. For detecting UAP1, primer and probe sets shown in SEQ ID NOS:138, 139, and 140, SEQ ID NOS:147, 148, and 149, and SEQ ID NOS:156, 157, and 158. For detecting PUS7, primer and probe sets shown in SEQ ID NOS:177, 178, and 179, SEQ ID NOS:183, 184, and 185, and SEQ ID NOS:189, 190, and 191. For detecting BCL6, primer and probe sets shown in SEQ ID NOS:102, 103, and 104, and SEQ ID NOS:108, 109, and 110.

[0138] The reagents for detecting the protein expression level of a marker gene may comprise an antibody that specifically binds to the protein encoded by the marker gene.

[0139] The kits may further comprise a carrier means being compartmentalized to receive in close confinement one or more container means such as vials, tubes, and the like, each of the container means comprising one of the separate elements to be used in the method. For example, one of the container means may comprise a probe that is or can be detectably labeled. Such probe may be an antibody or polynucleotide specific for a marker gene. Where the kit utilizes nucleic acid hybridization to detect the target nucleic acid, the kit may also have containers containing nucleotide(s) for amplification of the target nucleic acid sequence and/or a container comprising a reporter-means, such as a biotin-binding protein, such as

avidin or streptavidin, bound to a reporter molecule, such as an enzymatic, florescent, or radioisotope label.

[0140] The kit of the invention will typically comprise the container described above and one or more other containers comprising materials desirable from a commercial and user standpoint, including buffers, diluents, filters, needles, syringes, and package inserts with instructions for use. A label may be present on the container to indicate that the composition is used for a specific therapy or non-therapeutic application, and may also indicate directions for either *in vivo* or *in vitro* use, such as those described above.

[0141] The kit can further comprise a set of instructions and materials for preparing a tissue or cell sample and preparing nucleic acids (such as mRNA) from the sample.

[0142] The invention provides a variety of compositions suitable for use in performing methods of the invention, which may be used in kits. For example, the invention provides surfaces, such as arrays that can be used in such methods. In some embodiments, an array of the invention comprises individual or collections of nucleic acid molecules useful for detecting mutations of the invention. For instance, an array of the invention may comprises a series of discretely placed individual nucleic acid oligonucleotides or sets of nucleic acid oligonucleotide combinations that are hybridizable to a sample comprising target nucleic acids, whereby such hybridization is indicative of presence or absence of a mutation of the invention.

[0143] Several techniques are well-known in the art for attaching nucleic acids to a solid substrate such as a glass slide. One method is to incorporate modified bases or analogs that contain a moiety that is capable of attachment to a solid substrate, such as an amine group, a derivative of an amine group or another group with a positive charge, into nucleic acid molecules that are synthesized. The synthesized product is then contacted with a solid substrate, such as a glass slide, which is coated with an aldehyde or another reactive group which will form a covalent link with the reactive group that is on the amplified product and become covalently attached to the glass slide. Other methods, such as those using amino propyl silican surface chemistry are also known in the art, as disclosed at world wide web at cmt.corning.com and cmgm.stanford.edu/pbrown1.

[0144] Attachment of groups to oligonucleotides which could be later converted to reactive groups is also possible using methods known in the art. Any attachment to nucleotides of oligonucleotides will become part of oligonucleotide, which could then be attached to the solid surface of the microarray. Amplified nucleic acids can be further modified, such as

through cleavage into fragments or by attachment of detectable labels, prior to or following attachment to the solid substrate, as required and/or permitted by the techniques used.

[0145] The following are examples of the methods and compositions of the invention. It is understood that various other embodiments may be practiced, given the general description provided above.

EXAMPLES

Example 1. Identification of markers associated with responsiveness to treatment with anti-CD40 Ab.1 in clinical trials

Clinical Trial 001 (Phase II)

[0146] A multicenter, phase II, open-label study to determine the overall response rate and toxicity profile of anti-CD40 Ab.1 in patients with relapsed DLBCL. Tumor samples were assessed by a central lab for pathology confirmation and CD40 expression. Eligible patients had de novo or a transformed DLBCL at diagnosis and were excluded if there was a prior history of indolent lymphoma. Required prior therapy consisted of combination chemotherapy with rituximab and, if eligible, autologous stem cell transplantation. Patients received 6 IV infusions of anti-CD40 Ab.1 over 5 weeks (Cycle 1) with intra-patient dose loading (1 mg/kg on Day 1; 2 mg/kg on Day 4; 4 mg/kg on Day 8) and 8 mg/kg/wk thereafter. Responding patients and those with SD (stable disease) were eligible to continue therapy until disease progression or up to a maximum of 12 cycles. Tumor tissues were taken from patients before they received treatment with anti-CD40 Ab.1. For example, samples were taken as part of routine lymphoma diagnosis.

[0147] Anti-CD40 Ab.1 is a humanized IgG1 monoclonal antibody against CD40. It is produced in and secreted by a genetically engineered Chinese Hamster Ovary (CHO) cell line. The anti-CD40 Ab.1 has the following amino acid sequence:

[0148] *Heavy Chain* (SEQ ID NO:1). The italicized underlined ASN 294 residue identifies the location of the carbohydrate moiety.

EVQLVESGGG	LVQPGGSLRL	SCAASGYSFT	GYIHWVRQA	PGKGLEWVAR	50
VIPNAGGTSY	NQKFKGRFTL	SVDNSKNTAY	LQMNSLRAED	TAVYYCAREG	100
IYWWGQGTLV	TVSSASTKGP	SVFPLAPSSK	STSGGTAALG	CLVKDYFPEP	150
VTVSWNSGAL	TSGVHTFPAV	LQSSGLYSLS	SVVTVPSSSL	GTQTYICNVN	200
HKPSNTKVDK	KVEPKSCDKT	HTCPPCPAPE	LLGGPSVFLF	PPKPKDTLMI	250
SRTPEVTCVV	VDVSHEDPEV	KFNWYVDGVE	VHNAKTKPRE	EQYNSTYRVV	300
SVLTVLHQDW	LNGKEYKCKV	SNKALPAPIE	KTISKAKGQP	REPQVYTLPP	350
SREEMTKNQV	SLTCLVKGFY	PSDIAVEWES	NGQPENNYKT	TPPVLDSDGS	400
FFLYSKLTVD	KSRWQQGNVF	SCSVMEALH	NHYTQKSLSL	SPG	443

[0149] *Light Chain* (SEQ ID NO:2).

DIQMTQSPSS	LSASVGDRVT	ITCRSSQSLV	HSNGNTFLHW	YQQKPGKAPK	50
LLIYTVSNRF	SGVPSRFSGS	GSGTDFTLTI	SSLQPEDFAT	YFCSQTTHVP	100
WTFGQGTKVE	IKRTVAAPSV	FIFPPSDEQL	KSGTASVVCL	LNNFYPREAK	150
VQWKVDNALQ	SGNSQESVTE	QDSKDSTYSL	SSTLTLSKAD	YEKHKVYACE	200
VTHQGLSSPV	TKSFNRGEC				219

Clinical Trial 002 (Phase I)

[0150] Multi-institutional, multi-dose phase I study was conducted to test the safety, pharmacokinetic properties, immunogenicity, and antitumor activity of intravenous anti-CD40 Ab.1 in patients with relapsed NHL. Patients with multiple histologic subtypes of NHL were enrolled on this study, including diffuse large B-cell (DLBCL; 14), follicular (FCL; 9), mantle cell (MCL; 9), marginal zone (MZL; 2) and small lymphocytic (SLL; 1). Patients were treated with a dose-loading schedule: 1 mg/kg of anti-CD40 Ab.1 on day 1 and day 4 and subsequent intra-patient dose-escalation during weeks 2–5 to a maximum dose of 3, 4, 6, or 8 mg/kg over four cohorts. Subsequently, a rapid dose-loading schedule was tested in one cohort (40% increase in total anti-CD40 Ab.1 administered during cycle 1). Responding patients or those with stable disease were eligible for a second cycle, consisting of four consecutive weekly infusions at the cohort-specific maximum dose of anti-CD40 Ab.1. Eight patients with DLBCL completed cycle 1 and received a maximum dose of at least 3 mg/kg anti-CD40 Ab.1 with an objective response rate of 37.5% (i.e. 1 CR and 2 PR) and 2 SD. Additional objective responses were seen in one patient with MCL (CR) and one patient with MZL (PR). The median duration of response for these 5 patients has not yet been reached (range 8–37 weeks). Tumor tissues were taken from patients before they received treatment with anti-Cd40 Ab.1. For example, samples were taken as part of routine lymphoma diagnosis.

Clinical Sample Preparation and qRT-PCR

[0151] Formalin Fixed Paraffin Embedded (FFPE) archival tumor tissue from the Phase I and Phase II clinical trials described above was obtained from the clinical investigation sites with appropriate IRB approval and patient consent. 4-6 micron sections derived from the tumor tissue were mounted on glass slides and one slide for each case was subject to H&E staining using standard pathology laboratory protocol. A board certified Pathologist marked the H&E slide for tumor content and was used as a guide to macrodissect the remaining tumor-containing region for RNA extraction using the Ambion RecoverAll™ Total Nucleic Acid Isolation Kit for FFPE Tissues (Cat. No. AM1975; Applied Biosystems/Ambion, Austin, TX).

[0152] 450 ng total RNA per sample was reverse transcribed in a total reaction volume of 20 uL using Applied Biosystems' High Capacity Reverse Transcription cDNA Synthesis kit (Cat. No. 4368814; Applied Biosystems, Foster City, CA). Manufacturer's recommendations were followed with the exception of a shortened 60min RT reaction at 37 degrees. 5 ng total RNA equivalent cDNA (assuming 100% cDNA synthesis efficiency) product was mixed with Applied Biosystems' 2X Universal Master Mix (no UNG) in a volume of 15 uL for each PCR assay well. All amplifications were performed in triplicate in 384-well plates using a 2-step (95 degrees 15 sec, 60 degrees 1 min) PCR amplification procedure. Reactions were carried out to 40 cycles on a validated ABI 7900 real-time PCR system. Sequences of the primers and probes used are shown in Table 1.

Table 1. Primers and Probes

Gene Locus	GenBank Accession No.	Probe Overlap	Forward Primer	Reverse Primer	Probe
PRKCA	NM_002737.2	1	TGACAAAATGTAGAGGCCATTCA (SEQ ID NO:3)	CATCCGTCCTCTGCGATATAA (SEQ ID NO:4)	CCGTCAACACCATTT (SEQ ID NO:5)
IGF1R	NM_000875.3	1	TTGCAAGAGAAAGAAATTCAAACAC (SEQ ID NO:6)	TGCTTGAATCCATTGACTGCTT (SEQ ID NO:7)	ACAACAGCAGTAAGAAGA (SEQ ID NO:8)
BTG2	NM_006763.2	1	CAGTCCCTGCCCTTTTAGAAG (SEQ ID NO:9)	ATCATAAAGAAAGAAAGAGACAAGATT (SEQ ID NO:10)	AGCCTCATGGTCTCAT (SEQ ID NO:11)
LMO2	NM_005574.2	1	GGCCACAGCCCATCCA (SEQ ID NO:12)	CTTGCCCTAAATGTTCCCTTCT (SEQ ID NO:13)	AGTAACAGCATGATTAGC (SEQ ID NO:14)
CD22	NM_001771.2	1	TTTGGAGTGAGGCATTGCA (SEQ ID NO:15)	CCGGAGTCCCAGAGTCAA (SEQ ID NO:16)	AGACGTACGTATCAGCG (SEQ ID NO:17)
SMN1	NM_000344.2	1	CTGGAATGTGAAGCGTTATAGAAGAT (SEQ ID NO:18)	CCTTTTCTTCTCCCAACACTTGA (SEQ ID NO:19)	CTGGCCTCATTTCT (SEQ ID NO:20)
EPDR1	NM_017549.3	1	CAGCCTCTCTTGTCCTCGTT (SEQ ID NO:21)	TCCCTAGCAATGGACAAACTCA (SEQ ID NO:22)	CCTTATGTGTGAATGTGG (SEQ ID NO:23)
CD40	NM_001250.4	1	GGATCCTGTGTTGCCATCCT (SEQ ID NO:24)	GCTTCTTGGCCACCTTTTGTG (SEQ ID NO:25)	TTGGTGTGGTCTTT (SEQ ID NO:26)
IFTM1	NM_003641.3	1	GGCTTCATAGCATTCGCCACT (SEQ ID NO:27)	TCACGTGCGCAACCATCTT (SEQ ID NO:28)	CGTGAAGTCTAGGGACAG (SEQ ID NO:29)
VNN2	NM_004665.2	1	GACTTGATGTATGGGAGTGAGGAGT (SEQ ID NO:30)	TCTCTTCAAGGGCACAGCTATG (SEQ ID NO:31)	CAGGCCATTGCAA (SEQ ID NO:32)
PRPSAP2	NM_002767.2	1	GCCAAACTGGAACACATAAGAGTGA (SEQ ID NO:33)	GCATGACGGTTCCTGTGAAA (SEQ ID NO:34)	TGCTCGGTGGGATGG (SEQ ID NO:35)
PRKCA	NM_002737.2	1	CGGAGTTGAGGTTTTCCTT (SEQ ID NO:36)	GACGGTTGAATGGCCTCTACA (SEQ ID NO:37)	TGTATAAGCACCTACTGACA (SEQ ID NO:38)
IGF1R	NM_000875.3	1	AGGACTTCTTCATGGGTCTTACAGTT (SEQ ID NO:39)	AAGTGACATTAAAGACGATGTGTATGC (SEQ ID NO:40)	TGTTAGACCATGAAACATT (SEQ ID NO:41)
BTG2	NM_006763.2	1	CAGGCTGTGTTCTTGCATCTTG (SEQ ID NO:42)	GACCATGAGGCTGCTTCTAAAAA (SEQ ID NO:43)	CTGCAACAGGTCCCT (SEQ ID NO:44)
LMO2	NM_005574.2	1	TTGGACCAAGGGAACATG (SEQ ID NO:45)	GGTTAAAAAGTTGTGGTTTCCATTCTC (SEQ ID NO:46)	TGGAGACGATTTTCG (SEQ ID NO:47)
CD22	NM_001771.2	1	GACATCCCACTCAGGAATATTATG (SEQ ID NO:48)	CTGTCTTTTCTGGGCTTTCC (SEQ ID NO:49)	CCAGTTCTGCCTCTGA (SEQ ID NO:50)
SMN1	NM_000344.2	1	GGCATAGAGCAGCACTAAATGACA (SEQ ID NO:51)	TTCTATAACGCTTCACATTCAGATC (SEQ ID NO:52)	CACTAAAGAAACGATCAGAC (SEQ ID NO:53)
EPDR1	NM_017549.3	0	CGCACTTTGGCCTTCTTACA (SEQ ID NO:54)	TGGAAGGAGATGCAGAAAGTCAGA (SEQ ID NO:55)	CACTGCTCATACCTC (SEQ ID NO:56)

Gene Locus	GenBank Accession No.	Probe Overlap	Forward Primer	Reverse Primer	Probe
CD40	NM_001250.4	1	CCTGCCAGTCGGCTTCT (SEQ ID NO: 57)	GTCCAAGGGTGACATTTTTCG (SEQ ID NO: 58)	CTCCAATGTGTCTCATCTG (SEQ ID NO: 59)
IFITM1	NM_003641.3	1	GGTTTACTAGTAGCGGCCATA (SEQ ID NO: 60)	GCAGGGCCAGCATTCG (SEQ ID NO: 61)	CAACCTTGCACCTCCAC (SEQ ID NO: 62)
VNN2	NM_004665.2	1	TGTCATTTTGGTACTCTGA (SEQ ID NO: 63)	CCAAACACCCAGGCTCTT (SEQ ID NO: 64)	CAGTGTGAACAATG (SEQ ID NO: 65)
PRPSAP 2	NM_002767.2	0	GCTCCAGTGCCTCAAGATT (SEQ ID NO: 66)	CGACGGATCGCTCTGAA (SEQ ID NO: 67)	AAACTGTGATATCAGCATG (SEQ ID NO: 68)
PRKCA	NM_002737.2	0	TGGGCAACTCAGAAATACITCGA (SEQ ID NO: 69)	ACGTCAATAGGCACGTTTGCT (SEQ ID NO: 70)	CTCCCAAGATATAAGAGGC (SEQ ID NO: 71)
IGF1R	NM_000875.3	0	GTCCACCTCTCCCTTCT (SEQ ID NO: 72)	CACGCACTTAGTACAAAGCATAAGA (SEQ ID NO: 73)	CTCACTCAAGAAAC (SEQ ID NO: 74)
BTG2	NM_006763.2	0	CCCAACCGAATCACCTTAAGA (SEQ ID NO: 75)	CAGGAGGTGGCCATCCT (SEQ ID NO: 76)	ACAGGGTAGGGCAT (SEQ ID NO: 77)
LMO2	NM_005574.2	0	TCTCCATGGCATCTTCGTCCT (SEQ ID NO: 78)	ATCCCTTACCCACCCCTCAA (SEQ ID NO: 79)	ACTCTTAGGCACTTTGG (SEQ ID NO: 80)
CD22	NM_001771.2	0	CGCCTCAGGCACAAGAA (SEQ ID NO: 81)	GCAGCCCATCCAGTGTCAAT (SEQ ID NO: 82)	ATGTGGACTATGTGATCCT (SEQ ID NO: 83)
SMN1	NM_000344.2	0	CATGGTACATGAGTGGCTATCATACT (SEQ ID NO: 84)	GTGAGCACCTTCTTCTTTTGA (SEQ ID NO: 85)	CTATTATATGGGTTTCAGAC (SEQ ID NO: 86)
EPDR1	NM_017549.3	0	GACTATTCTCTCTAAACCCAGGACT (SEQ ID NO: 87)	CCCAGTGCATTTAATGACCAAA (SEQ ID NO: 88)	AGTTCCCTCGTACTGTC (SEQ ID NO: 89)
CD40	NM_001250.4	1	ATCAATTTTCCGACGATCTTC (SEQ ID NO: 90)	CGGTTGGCATCCATGTAAAGT (SEQ ID NO: 91)	TGGCTCCAACACTG (SEQ ID NO: 92)
IFITM1	NM_003641.3	0	AGTCCACCGTGATCAACATC (SEQ ID NO: 93)	CAGGGACCAAGACGACATGTT (SEQ ID NO: 94)	ACAGCGAGACCTCCGT (SEQ ID NO: 95)
VNN2	NM_004665.2	0	CAACTTGTGGACGGCCAGTA (SEQ ID NO: 96)	GTGCCACTGAGGGAGAACATTT (SEQ ID NO: 97)	AAACTGCTTCTACAAGATT (SEQ ID NO: 98)
PRPSAP 2	NM_002767.2	0	CAGCAGAGACCTGAGGAGAA (SEQ ID NO: 99)	CAAGCCATGAGTTGCCATCA (SEQ ID NO: 100)	AGGTGCATATAAGATCTT (SEQ ID NO: 101)
BCL6	NM_001706.2	1	CCCATTCGCGTCATGCTT (SEQ ID NO: 102)	AATGCAGTTTAGACACAGCCAAAC (SEQ ID NO: 103)	TGTTATACTACTCCGGAGA (SEQ ID NO: 104)
LRRC8A	NM_019594.2	1	AGTTCAGCCAGATGGAAGGT (SEQ ID NO: 105)	GCGGCATCGTAAATAAGGA (SEQ ID NO: 106)	TTCAGGGAAGGTGGGC (SEQ ID NO: 107)
BCL6	NM_001706.2	1	CACAGGACTTGAAGTTGTTACTAAC (SEQ ID NO: 108)	TGACGCAGATGGGATGAGA (SEQ ID NO: 109)	CTCTCTTTGGGAATGTT (SEQ ID NO: 110)
LRRC8A	NM_019594.2	0	CAAAGCAGCAGACGTTGAAC (SEQ ID NO: 111)	CACACCAGATCGGAAGACA (SEQ ID NO: 112)	TTTCCCTGGGCGCAGG (SEQ ID NO: 113)

Gene Locus	GenBank Accession No.	Probe Overlap	Forward Primer	Reverse Primer	Probe
RGS13	NM_144766.1	0	GGGATTCCCTACCCAGATTCTTA (SEQ ID NO:114)	CAGAAACTGTTGTTGGACTGCATAG (SEQ ID NO:115)	ACTCAGAAATCTACCAAAAA (SEQ ID NO:116)
YIPF3	NM_015388.2	1	TGAGCTGTAGTGCCTAAGTACCT (SEQ ID NO:117)	GGCCTTGTGCCTTTCAGAAG (SEQ ID NO:118)	CTTGATGCCGTGTCGGC (SEQ ID NO:119)
YIPF3	NM_015388.2	1	TGGCTGCCCTACACATGCT (SEQ ID NO:120)	CAGGATCCCTCTACACATTG (SEQ ID NO:121)	CCTGCTCTATCTGCATTT (SEQ ID NO:122)
YIPF3	NM_015388.2	0	GAGGCTCAGTGTGATTGACAT (SEQ ID NO:123)	CACCCATATCTCGAAGCTAGAG (SEQ ID NO:124)	AGAACATGGATGATACCTC (SEQ ID NO:125)
RGS13	NM_144766.1	0	TCCAGCCACAGTCCCTCTAGA (SEQ ID NO:126)	TCCTGAATGTTCTGATGATAGTCTCT (SEQ ID NO:127)	AGATTAACATGACAGTTG ACA(SEQ ID NO:128)
EPDR1	NM_017549.3	0	CGAGAGGAGGCGCTGATC (SEQ ID NO:129)	ACATCACTCCATCCTTATACAGCAAA (SEQ ID NO:130)	CCTGCAAGAGATTATTT (SEQ ID NO:131)
EPDR1	NM_017549.3	0	GGATCCTCTTGACATTCTCTCAAA (SEQ ID NO:132)	GGCCCCCGATGGA (SEQ ID NO:133)	CTCCACCTTTGAAGACC (SEQ ID NO:134)
EPDR1	NM_017549.3	0	CGAGGCTGCGGCATATGA (SEQ ID NO:135)	GAACAGGCATTAGAAATACCCAAAG (SEQ ID NO:136)	TGACTAGATGGCTAAATATG (SEQ ID NO:137)
UAP1	NM_003115.4	0	CTACTGCAAGGATGCTTTGAT (SEQ ID NO:138)	TGGCCCCCTGTCATGA (SEQ ID NO:139)	TCCCTTCATCATGTGCTG (SEQ ID NO:140)
CD79B	NM_000626.2	0	GCCGGTGAGTTACACGTT (SEQ ID NO:141)	CCCCAAACCCGTGACAAC (SEQ ID NO:142)	CCTCCAAGGAGCTC (SEQ ID NO:143)
CLPTM1	NM_001294.1	1	CAAGGCCCTCAACACATTCA (SEQ ID NO:144)	GGTACATAACGGGCATCTTGATG (SEQ ID NO:145)	ACCTGTTGCGCTTTG (SEQ ID NO:146)
UAP1	NM_003115.4	1	CCTATGCTGGAGAAGGATTAGAAAGT (SEQ ID NO:147)	CGATCATTAGAGTGCATGGAA (SEQ ID NO:148)	ATGTGGCAGATAAAG (SEQ ID NO:149)
CD79B	NM_000626.2	0	TCTCGCCACCCCTCACCAT (SEQ ID NO:150)	GCTGACAGAAAGTAGATGCCATTGT (SEQ ID NO:151)	CAAGGCATCCGGTTTG (SEQ ID NO:152)
CLPTM1	NM_001294.1	0	AAGTCGCCCTGGAACCTCCT (SEQ ID NO:153)	CACCGAGTCCCTGCTCCTCAT (SEQ ID NO:154)	ATGAGTTGTACGAGCAGTC (SEQ ID NO:155)
UAP1	NM_003115.4	1	CATGAGCTGGTGAATAAATGGTATTT (SEQ ID NO:156)	AAAGCTATTCTTCATCGTGGCAAA (SEQ ID NO:157)	AACAGATACCAAGTTTT (SEQ ID NO:158)
CD79B	NM_000626.2	1	TCCCCAGCTCTGCCAAAG (SEQ ID NO:159)	CAGAGAACTCCCTCCAAGTTGCT (SEQ ID NO:160)	CTGGAGTAGAAGACACACAG (SEQ ID NO:161)
CLPTM1	NM_001294.1	0	GGCAGGCCAGGGTTTGT (SEQ ID NO:162)	CGAGATGGCTGGAACACAGA (SEQ ID NO:163)	AGCGCTGTCTGTC (SEQ ID NO:164)
CTSC	NM_001814.3	1	GACTCAGCCTCTGGGATGGA (SEQ ID NO:165)	GGATCCGGAAGTAGCCATTCT (SEQ ID NO:166)	TGGATTGTTAAAAACAGCTG G (SEQ ID NO:167)
CTSC	NM_001814.3	0	AGCGGCTTCCCATACCT (SEQ ID NO:168)	CTTCTTCCACAGCCCAAAA (SEQ ID NO:169)	ATTGCAGGAAGTACGCC (SEQ ID NO:170)

Gene Locus	GenBank Accession No.	Probe Overlap	Forward Primer	Reverse Primer	Probe
CTSC	NM_001814.3	0	CCCAACCTGCACCACTGA (SEQ ID NO:171)	CAAGATGTTGGCAAAATGCAAA (SEQ ID NO:172)	CTGAAATACAGCAAAAGA (SEQ ID NO:173)
CD44	NM_000610.3	0	CCTTTGCGCATTTATTCATCAGT (SEQ ID NO:174)	GCTTCTATGACAAGCAGCCTTTG (SEQ ID NO:175)	AGGGTCCGATTGG (SEQ ID NO:176)
PUS7	NM_019042.3	0	CTCTGTAGCACACGGCTGGATTG (SEQ ID NO:177)	AGGCTGCAGTCAAGATTGA (SEQ ID NO:178)	AGTGCAATCCTGCAATT (SEQ ID NO:179)
CD44	NM_000610.3	0	CCACTTGGAGGCCTTTCATC (SEQ ID NO:180)	AGGTTGGCGATCAGGAATACA (SEQ ID NO:181)	TCGGGTGCTATGGA (SEQ ID NO:182)
PUS7	NM_019042.3	0	CCTTGCTGGTTTCGATGTT (SEQ ID NO:183)	GAGCATTTCCCTGTAGGTTCTT (SEQ ID NO:184)	CCCAAGCATAAAATT (SEQ ID NO:185)
CD44	NM_000610.3	0	CAACCGTTGGAAACATAACCAATT (SEQ ID NO:186)	AACAATCAGTAGCACATTGCATCTG (SEQ ID NO:187)	AGGAGCTGGGACACT (SEQ ID NO:188)
PUS7	NM_019042.3	0	TGGACTCACTGAGGCTGACGTA (SEQ ID NO:189)	GATTCGCCGAGAACCCTTGATG (SEQ ID NO:190)	TCACCAAGTTGTGAGTTC (SEQ ID NO:191)
RPL22	NM_000983.3	1	GCTGCCAATTTTGAGCAGTTT (SEQ ID NO:192)	GTTCCAGCTTTCCGTTCA (SEQ ID NO:193)	TGCAAGAAAGGATCAAA (SEQ ID NO:194)
LOC728179	XR_015348.1	1	TCTTGCTGCCCTGTGTG (SEQ ID NO:195)	TGCCTTCCCTTAATAATGCA (SEQ ID NO:196)	AAAATGGGGTCCCTT (SEQ ID NO:197)
SERBP1	NM_001018067.1	1	CTCCCGTACACAGAAAGTAACAAA (SEQ ID NO:198)	AAAACATCCCTGCTACCAATACATT (SEQ ID NO:199)	ATGGTAGTCAGTTTGTATT (SEQ ID NO:200)
RPL9	NM_000661.4	1	TCCGTTACAAGATGAGGCTGTGT (SEQ ID NO:201)	CATTCTCCTGGATAACAACGTTGA (SEQ ID NO:202)	TGCTCACTTCCCC (SEQ ID NO:203)
CFL1	NM_005507.2	1	TCCATCCCTTGACGGTTCTG (SEQ ID NO:204)	AGCCCAAGAGGAATCAAAAGATC (SEQ ID NO:205)	CCTTCCCAACTGCTTT (SEQ ID NO:206)
RPL13	NM_000977.2	1	GAGTCATCACTGAGGAGAGAGAAGAAAT (SEQ ID NO:207)	TGGCAGGGGCCATAGG (SEQ ID NO:208)	CAAAGCCTCGCTAGTC (SEQ ID NO:209)
FLJ16025	NM_198505.1	1	CCTACACCCCTTATCCCCTACT (SEQ ID NO:210)	CCAGGGCTATTGGTTGAATGA (SEQ ID NO:211)	TTATTATCGAAACCATCAGC (SEQ ID NO:212)
RPS10	NM_001014.3	1	CGACCTGGAGACTCACAAG (SEQ ID NO:213)	GGCACAGCACTCCGTCTGT (SEQ ID NO:214)	AAGCTGACAGAGATACC (SEQ ID NO:215)
NPM1	NM_002520.5	1	TCTGGCTGTCCTTTTATAATGCA (SEQ ID NO:216)	CTTGGCAATAGAACCTGGACAAC (SEQ ID NO:217)	AGTGAGAACTTTCCC (SEQ ID NO:218)
CCDC72	NM_015933.3	1	GCAAGAGAAGCCACTGAAACA (SEQ ID NO:219)	GAAAGCCTTATCTTCTCCTCGTCCAT (SEQ ID NO:220)	CCCAAGAACGAGGCCA (SEQ ID NO:221)
RPS19	NM_001022.3	1	GGCTGAAATGGTGGAAAAGG (SEQ ID NO:222)	CTTTGTCCCTGAGGTGTGAGTTT (SEQ ID NO:223)	CCAAGATGGGGCCG (SEQ ID NO:224)
RPS16	NM_001020.4	1	TGTGGATGAGGCTTCCAAGAA (SEQ ID NO:225)	CAGCAGGGTCCGGTCATACACT (SEQ ID NO:226)	AGATCAAGACATCCTCATC (SEQ ID NO:227)

Gene Locus	GenBank Accession No.	Probe Overlap	Forward Primer	Reverse Primer	Probe
EEF1G	NM_001404.4	1	GGCAGGTGGACTACGAGTCATAC (SEQ ID NO:228)	GTCTCCCTCGCTGCCAGGAT (SEQ ID NO:229)	CATGGCGGAAACTG (SEQ ID NO:230)
RPS5	NM_001009.3	1	CCGGAACATTAAGACCATTCG (SEQ ID NO:231)	CCCTTGGCAGCATTGAIGA (SEQ ID NO:232)	AGTGCCTGGCAGATG (SEQ ID NO:233)
EEF1A1	NM_001402.5	1	CTGCCACCCCACTCTTAATCA (SEQ ID NO:234)	GGCCAATTGAACAAACAGTTCT (SEQ ID NO:235)	TGGTGGAGAACGGTC (SEQ ID NO:236)
RPL28	NM_000991.3	1	GGAAGCCTGCCACCTCCTAT (SEQ ID NO:237)	TGGCGCGAGCATTTCTTG (SEQ ID NO:238)	TGCGGACCCCATC (SEQ ID NO:239)
ACTG1	NM_001614.2	1	TGTCCTTGAAGCTTGATCTGATATC (SEQ ID NO:240)	TTCAATACAAAGGTCAAAATCAGCAA (SEQ ID NO:241)	CACTGGATTGTAGAACTT (SEQ ID NO:242)
BTF3	NM_001037637.1	1	AGCCTCAGATGAAAGAAACAATCA (SEQ ID NO:243)	CACCTTGTGCTGCAGTTTGG (SEQ ID NO:244)	AACCAGGAAAAACTC (SEQ ID NO:245)
TMSB4X	NM_021109.2	1	AAGCAGCGAATCGTAATGAG (SEQ ID NO:246)	TGCTTGTGGAATGTACAGTGCAT (SEQ ID NO:247)	CGTGGCGGCCAA (SEQ ID NO:248)
TPM3	NM_153649.3	1	CCCTTTCTGGGTTTGAAGCT (SEQ ID NO:249)	CTGACTGATACAAAGCACAATTGAGA (SEQ ID NO:250)	CTGTCTCTAGAAGTGCC (SEQ ID NO:251)
USMG5	NM_032747.2	1	GCTGTGAAAGCAACATAAATGGAT (SEQ ID NO:252)	GGCATGGGAACTTAACAGATGAG (SEQ ID NO:253)	TAAACTGTCTACGGTTCTT (SEQ ID NO:254)
EIF1	NM_005801.3	1	CGCTATCCAGAACCTCCACTCT (SEQ ID NO:255)	CAGGTCAATCACCTTACTTGCA (SEQ ID NO:256)	TCGACCCCTTGCTG (SEQ ID NO:257)

Data Processing

[0153] The raw qRT-PCR as results were pre-processed according to the description below under Normalization, Transformation, and Imputation and the Sensitivity Index was computed as described under Sensitivity Index and Classifier. Spearman's rank correlations were used for correlation estimates and corresponding P-values. For the Multivariate Sensitivity Index, probes were selected and coefficients estimated using the elastic net blend of lasso (L1) and ridge (L2) penalized regression, as described by Zhou et al., Statist. Soc. B. 67:301-320, 2005 and implemented by Friedman, Hastie and Tibshirani, Regularization Paths for Generalized Linear Models via Coordinate Descent. Technical Report, Dept. of Statistics, Stanford University at www-stat.stanford.edu/~hastie/Papers/glmnet.pdf. X^2 tests were used to test for associations among categorical variables.

Normalization, Transformation and Imputation

[0154] The following are definitions for assay data and model parameters:

Definitions**Assay Data**

ℓ	=	a reference set of samples (e.g. NHL cell lines)
N_ℓ	=	sample size
p	=	number of probes (not including normalizers)
$N_{\ell j}^{(Obs)}$	=	detected sample size for probe j
$N_{\ell j}^{(ND)}$	=	not detected sample size for probe j
$y_{ij}^{(Obs)}$	=	detected raw assay value for sample i , probe j
$p_i^{(nrm.Obs)}$	=	number of detected normalizer values for sample i
$y_{ij}^{(nrm.Obs)}$	=	detected normalizer value for sample i , probe j

Model Parameters

$\hat{\mu}_{\ell j}^{(Obs.raw)}$	=	set ℓ mean of detected $\log_2$ assay values for probe j (un-normalized)
$\hat{\sigma}_{\ell j}^{(Obs)}$	=	set ℓ standard deviation of detected $\log_2$ assay values for probe j
$\gamma_\ell^{(ND)}$	=	set ℓ number of standard deviations above the mean

For a reference set of samples, such as that used to fit index coefficients and classifier cutoffs, mean and standard deviation model parameters are computed using the reference set data (refer to the formulas for Reference Set Model Parameters below). For new samples, for example a single new sample for which the index and class are to be computed, model parameters must be taken from a reference set, ℓ , which is chosen to be the most representative of the population from which the new sample is drawn. For example, a

clinical reference set for each indication and line of therapy in which the assay is used may be maintained. The formulas for calculating reference set model parameters and transformed, normalized assay values are shown below.

Formulas

Reference Set Model Parameters

Intermediate values

$$\hat{\mu}_i^{(nrm.Obs)} = \frac{1}{p_i^{(nrm.Obs)}} \sum_{j=1}^{p_i^{(nrm.Obs)}} y_{ij}^{(nrm.Obs)} \text{ (sample normalization factor)}$$

$$\hat{\mu}_{\ell j}^{(Obs)} = \frac{1}{N_{\ell j}^{(Obs)}} \sum_{i=1}^{N_{\ell j}^{(Obs)}} \left[\log_2 \left(y_{ij}^{(Obs)} \right) - \log_2 \left(\hat{\mu}_i^{(nrm.Obs)} \right) \right] \text{ (normalized mean)}$$

Model parameters

$$\hat{\sigma}_{\ell j}^{(Obs)} = \sqrt{\frac{1}{N_{\ell j}^{(Obs)}} \sum_{i=1}^{N_{\ell j}^{(Obs)}} \left(\log_2 \left(y_{ij}^{(Obs)} \right) - \log_2 \left(\hat{\mu}_i^{(nrm.Obs)} \right) - \hat{\mu}_{\ell j}^{(Obs)} \right)^2}$$

$$\hat{\mu}_{\ell j}^{(Obs.raw)} = \frac{1}{N_{\ell j}^{(Obs)}} \sum_{i=1}^{N_{\ell j}^{(Obs)}} \log_2 \left(y_{ij}^{(Obs)} \right)$$

Transformed, Normalized Assay Values

Intermediate values

$$\hat{\mu}_i^{(nrm.Obs)} = \frac{1}{p_i^{(nrm.Obs)}} \sum_{j=1}^{p_i^{(nrm.Obs)}} y_{ij}^{(nrm.Obs)} \text{ (sample normalization factor)}$$

Transformed, normalized, imputed assay values

$$x_{ij}^{(Obs)} = - \left[\log_2 \left(y_{ij}^{(Obs)} \right) - \log_2 \left(\hat{\mu}_i^{(nrm.Obs)} \right) \right], \quad i = 1, \dots, N_{\ell j}^{(Obs)}$$

$$x_{ij}^{(ND)} = - \left[\hat{\mu}_{\ell j}^{(Obs.raw)} - \log_2 \left(\hat{\mu}_i^{(nrm.Obs)} \right) + \gamma_{\ell}^{(ND)} \hat{\sigma}_{\ell j}^{(Obs)} \right], \quad i = 1, \dots, N_{\ell j}^{(ND)}$$

The completed $N_{\ell} \times p$ matrix of values, $\begin{bmatrix} \mathbf{x}_1^{(Obs)} & \dots & \mathbf{x}_p^{(Obs)} \\ \mathbf{x}_1^{(ND)} & \dots & \mathbf{x}_p^{(ND)} \end{bmatrix}$, is input to the sensitivity index and classifier calculations.

Sensitivity Index and Classifier

[0155] The following are definitions for assay data and model parameters:

Definitions

Assay Data

- ℓ = a reference set of samples (e.g. NHL cell lines)
- N_ℓ = sample size
- p = number of probe pairs
- x_{ij} = transformed, normalized assay value for sample i , probe j
- $x_{ij'}$ = as above with j' the anti-correlated pair probe to probe j

Model Parameters

- $\beta_{\ell j}$ = set ℓ coefficient for probe j
- $\hat{\mu}_{\ell j}$ = set ℓ mean of transformed normalized assay values for probe j
- $\hat{\sigma}_{\ell j}^2$ = set ℓ mean of transformed normalized assay values for probe j
- C_ℓ = classification cutpoint

The formulas for calculating reference set model parameters and sensitivity index and classifier are shown below.

Formulas

Reference Set Model Parameters

Probe Means and Standard Deviations

$$\hat{\mu}_{\ell j} = \frac{1}{N_\ell} \sum_{i=1}^{N_\ell} x_{ij}$$

$$\hat{\sigma}_{\ell j}^2 = \frac{1}{N_\ell} \sum_{i=1}^{N_\ell} (x_{ij} - \hat{\mu}_{\ell j})^2$$

Index and Classifier

Sensitivity Index

$$S_{\ell i} = \sum_{j=1}^p \beta_{\ell j} \frac{x_{ij} - \hat{\mu}_{\ell j}}{\sqrt{\hat{\sigma}_{\ell j}^2}} - \beta_{\ell j'} \frac{x_{ij'} - \hat{\mu}_{\ell j'}}{\sqrt{\hat{\sigma}_{\ell j'}^2}}$$

Sensitivity Class

$$T_{\ell i} = \begin{cases} 1 \equiv \text{sensitive} & \text{if } S_{\ell i} \geq C_\ell \\ 0 \equiv \text{resistant} & \text{otherwise} \end{cases}$$

Clinical Trial 001 Results

[0156] Table 2 below provides a sample accounting of assayed specimens and clinical samples from Clinical Trial 001. Twenty nine archival FFPE tumor specimens from 24 patients with DLBCL were submitted for qRT-PCR processing. Three patients had multiple specimens and all 24 patients had usable qRT-PCR results for at least one specimen. Of these 24, 21 had tumor sum of the product of diameters (SPD) measurements reported both at baseline and at least one post-baseline visit.

Table 2: Clinical Trial 001 Sample Accounting

Diagnostic Assay			Clinical Database	
Archival FFPE specimens	29	Analysis sample size (both qRT-PCR and SPD available)		
# of patients (3 with multiple specimens)	24			
Specimens qRT-PCR Reported	27			
Usable qRT-PCR results (1 insufficient)	26		46	Patients in clinical database
qRT-PCR for unique patients (2 patient specimen pairs averaged together)	24	21	39	SPD Change from Baseline Reported

[0157] Table 3 summarizes the pairwise Spearman's rank correlations between the Main and Pair genes that contribute to the sensitivity index. Based on the cell line development samples, genes with low expression in particular groups of patient should be expected to have relatively high expression of the corresponding pair, on average, providing for self-normalization and the interpretation of the Sensitivity Index as a ratio of up- to down-regulated expression pathways (i.e. on a log base 2 scale). The magnitude of the correlations between pairs in this first clinical sample are statistically significant and notable high throughout, with the lower correlation estimate being -0.67 (P=0.0004). These tests alone constitute an independent confirmation that the assay target sequences are expressed in tumor

samples from this clinical population in-vitro and that the assay is detecting expression in the archived FFPE tissue samples.

Table 3: Main and Pair Gene Anti-correlations (N=21)

Main Gene*	Locus Link	Correlation Gene	Pair
IFITM1	8519	-.85	BTG2
CD40	958	-.84	IGF1R
RGS13	6003	-.70	CD44
VNN2	8875	-.87	CTSC
LMO2	4005	-.67	EPDR1
CD79B	974	-.75	UAP1
CD22	933	-.83	PUS7
* CD40, RGS13, VNN2, LMO2, CD22, BTG2, and UAP1 are genes with higher expression in sensitive cell lines.			

[0158] Table 4 summarizes the associations between the measurements for each probe individually and the largest reduction (or smallest increase) in tumor SPD post-baseline. Since rank correlations are based upon the difference (or ratio) of post-baseline to baseline measurements, positive correlations mean that higher expression of the probe is associated with tumor increases, on average; and the negative correlations mean that higher expression of the probe is associated with tumor decreases on average. Notably, all Main-Pair probe pairs have opposite-direction associations with SPD. The P-values are consistent with a promising trend in this sample. All P-values are below .5 (50% expected when there is no true association). All ranges are calculated as bootstrap 95th percentile confidence intervals, based upon 5,000 replicates sampled with replacement from the DLBCL patient sample, N=21. Narrower ranges will become available as the sample size increases. Since no model-building or checking was required to produce these results, they comprise a robust trend, which confirms that these qRT-PCR probe measurements are associated, overall, with reduction in tumor SPD in patients treated with anti-CD40 Ab.1.

Table 4: Associations between SPD and Individual Probe Measurements (N=21)

Main Gene	Rho.	P	Range	Pair Gene	Rho.	P	Range
IFITM1	+0.29	0.20	(-0.13, 0.68)	BTG2	-0.27	0.23	(-0.70, 0.19)
CD40	-0.16	0.49	(-0.58, 0.30)	IGF1R	+0.33	0.15	(-0.17, 0.73)
RGS13	-0.32	0.16	(-0.66, 0.13)	CD44	+0.34	0.14	(-0.11, 0.70)

VNN2	-0.26	0.26	(-0.67, 0.21)	CTSC	+0.31	0.17	(-0.17, 0.68)
LMO2	-0.25	0.27	(-0.69, 0.25)	EPDR1	+0.27	0.23	(-0.22, 0.67)
CD79B	+0.22	0.34	(-0.22, 0.61)	UAP1	-0.22	0.35	(-0.59, 0.22)
CD22	-0.25	0.28	(-0.66, 0.21)	PUS7	+0.20	0.39	(-0.26, 0.66)

[0159] The multivariate sensitivity index is a weighted average of the probes in Tables 3 and 4. Since weights in cell lines were not expected to reflect optimal weights in patient tumor specimens, the weights in cell lines were restricted to 1 and -1, corresponding to the signed, equal-weighted average, where the signs matched the association between each probe and resistance to anti-CD40 Ab.1 by IC25 in the cell lines. For clinical populations, new weights are required. As a preliminary analysis based upon 21 samples only, we chose to use a penalized, multivariate regression procedure to select and estimate weights for the best 8 of the 14 probes. Those weights (coefficient) are shown in Table 5, and the association between the resulting Sensitivity Index and SPD change from baseline is depicted in Figure 2. Larger multivariate Sensitivity Index values are associated with SPD decreases post-baseline (Spearman's Rho = -0.58, P=0.006). All ranges in Tables 4, 5, and 6 were calculated as bootstrap 95th percentile confidence intervals, based upon 5,000 replicates sampled with replacement from the DLBCL patient sample, N=21. Narrower ranges will become available as the sample size increases.

Table 5: Weights for the Multivariate Sensitivity Index (N=21)

Main Gene	Coeff.	Range	Pair Gene	Coeff.	Range
IFITM1	-0.08	(-11.7, 3.7)	BTG2	-0.62	(-11.6, 0.0)
CD40	0	(-9.5, 8.2)	IGF1R	0	(-9.0, 5.6)
RGS13	+1.13	(-1.9, 8.0)	CD44	-3.39	(-11.9, 0.0)
VNN2	0	(-4.1, 4.1)	CTSC	0	(-8.8, 2.1)
LMO2	0	(-8.5, 2.1)	EPDR1	-0.74	(-4.7, 3.6)
CD79B	+0.04	(-3.2, 9.0)	UAP1	-2.45	(-15.1, 0.0)
CD22	+0.63	(-0.0, 12.7)	PUS7	0	(-7.7, 7.3)

[0160] Using 26 samples from Clinical Trail 001, ranges for μ_j and σ_j values obtained are as shown in Table 6.

Table 6: μ_j and σ_j ranges based on data from Clinical Trail 001

μ_j	IFITM1	LMO2	CD40	VNN2	IGF1R	BTG2	CD22	BCL6
lower	-4.89	-5.09	-5.09	-5.10	-5.12	-5.02	-5.03	-5.07
upper	-4.79	-5.00	-5.02	-5.02	-5.06	-4.92	-4.93	-4.99

μ_j	RGS13	EPDR1	CD79B	UAP1	CTSC	CD44	PUS7
lower	-5.14	-5.19	-5.10	-5.26	-5.04	-4.97	-5.24
upper	-5.00	-5.12	-5.04	-5.18	-4.95	-4.87	-5.16

σ_j	IFITM1	LMO2	CD40	VNN2	IGF1R	BTG2	CD22	BCL6
lower	0.10	0.09	0.07	0.08	0.06	0.09	0.09	0.08
upper	0.17	0.14	0.12	0.13	0.10	0.15	0.14	0.12

σ_j	RGS13	EPDR1	CD79B	UAP1	CTSC	CD44	PUS7
lower	0.14	0.07	0.06	0.08	0.09	0.09	0.08
upper	0.22	0.11	0.10	0.12	0.14	0.16	0.12

Clinical Trial 002 Results

[0161] Raw qRT-PCR results were successfully generated for 10 patients with archival specimens. For those 10 patients, diagnosis, treatment group, multivariate sensitivity index, clinical response and SPD change from baseline are shown in Table 7. The multivariate sensitivity index weights were taken from the 21 Clinical Trial 001 patients (Table 5), so that these patients constitute a very small validation set. 2 of 4 patients with Sensitivity Index ≥ 0 exhibited some tumor shrinkage after anti-CD40 Ab.1 exposure and 4 of 6 patients with Sensitivity Index < 0 exhibited either tumor increase or a best response of PD (SPD was unavailable for 2 patients, but a best clinical response outcome was available for this patient).

Table 7. Summary of diagnosis, treatment group, multivariate sensitivity index, clinical response and SPD change for 6 patients in Clinical Trial 002.

Samples	Dx.	Treatment Group	Sensitivity Index	Best Response	SPD Percent Change
066-0001	MCL	Pre-2	+0.01	PD	+72.48
066-0015	MCL	V	-0.87	PD	+64.07
066-0009	DLBCL	III	+1.06	PR	-78.02
066-0006	DLBCL	I	-2.31	PR	-66.44
066-0011	T-Cell-LBCL	IV	-0.46	SD (PR)	-10.34
066-0005	DLBCL	I	-2.99	PD	+1,208.94
066-0013	MCL	IV	-3.67	PD	+94.59
066-0019	DLBCL	V	+0.15	SD	-32.64
066-0004	DLBCL	I	-0.46	PD	?
066-0002	DLBCL	Pre-2	+0.99	PD	?

[0162] BCL6. The qRT-PCR assay contains a 15th probe for the BCL6 gene. Though not currently used in the multivariate Sensitivity Index, it was a previously identified potential predictor of response to anti-CD40 Ab.1. As shown in Figure 3, while not significantly associated with SPD change in the combined DLBCL patient sample ($P=0.25$, $N=26$), BCL6 trends lower in those with tumor increases ($\rho=-0.23$).

Example 2. Use of 15 gene markers to determine responsiveness of DLBCL patients to treatment with anti-CD40 Ab.1

[0163] Using DLBCL patient samples from Phase I (11 samples) and Phase II (28 samples) clinical trials described in Example 1, a classifier based on qRT-PCT was developed for tumor size reduction of at least 10%, herein defined as anti-CD Ab.1 sensitive, using weighted K-nearest neighbors (KNN), with weights for the 15 markers (UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B) determined using penalized regression (GLMNET). Model parameters were determined by cross-validation and robust p-values were computed via permutation tests.

[0164] Using weighted K-nearest neighbors (WKNN), a class was assigned for a new sample using the known classes of the K nearest reference samples, where K is an integer between 4 and 13. The nearest reference samples (nearest neighbors) are those with the smallest weighted average of the absolute differences (WAAD) between each of the 15 probe measurements for UAP1, BTG2, CD40, VNN2, RGS13, CD22, LMO2, IFITM1, CTSC, CD44, PUS7, BCL6, EPDR1, IGF1R and CD79B, where the differences are between the probe measurements of new sample to be classified and those from each reference sample. The weights for the WAAD are the absolute values of the coefficients from an elastic net penalized regression of reference sample tumor shrinkage on the 15 probe measurements. The magnitude of the penalty is chosen by 10 fold cross-validation to minimize the WKNN classification error. The optimal K was determined as 5 in the 10-fold cross validation on the training dataset. Note that the weight for some probe measurements may be 0 (zero), so that not all probe measurements necessarily contribute to the classification, and relative contributions depend upon the reference sample probe measurements and their known classes. To determine the predicted class of a new sample, the K nearest reference samples contribute the inverse of their WAAD (i.e. 1 divided by the WAAD) in the manner of a vote for their known class labels. The class label with the largest total inverse WAAD contributions is assigned to the new sample. A prior class weight between 0 and 1, with

weights for all classes summing to 1 (one) may be used as a multiplier of the normalized inverse WAAD contributions to increase or decrease the proportion of new samples classified to each class. Similar results were obtained using unweighted KNN.

[0165] qRT-PCT was performed for all 15 genes using primers and probes described in Example 1 for the patient samples. For a specific sample of 39 DLBCL patients, the weights were determined for each of the 15 marker gene (Table 8).

Table 8. Weights for the Marker Genes

BCL6	IFITM1	CD40	RGS13	VNN2	LMO2	CD79B
1.98010348	1.75845322	0.00000000	0.00000000	0.00000000	0.00000000	0.00000000

CD22	BTG2	IGF1R	CD44	CTSC	EPDR1	UAP1
0.05014746	0.00000000	0.35155187	5.33314459	0.00000000	1.55417748	7.13145292

PUS7
0.00000000

[0166] Based on the method described above, a sample from the 39 patients was determined as Dx negative (non-responsive to the anti-CD40 Ab.1 treatment) or Dx positive (at least 10% tumor reduction in response to the anti-CD40 Ab.1 treatment). Data shown in Figure 4 indicate that an overall accuracy for predicting responsiveness to the anti-CD40 Ab.1 treatment are 79.5% (P=0.004). Twenty one of 24 signature negative patients (88%) displayed no measurable tumor shrinkage in response to the anti-CD40 Ab.1 treatment. Ten of 15 signature positive patients (67%) displayed significant tumor shrinkage in response to the anti-CD40 Ab.1 treatment. In addition, as shown in Figure 5, Dx positive patients had an increased progression free-survival. This is consistent with the observed tumor shrinkage. The progression-free survival (PFS) of the signature positive patients (predicted to respond) was significantly prolonged compared to the signature negative patients, with a median PFS of 169 days vs. 40 days, respectively (p=0.001). These data indicate that a 15-gene qRT-PCR DLBCL tumor signature was effective in predicting outcomes following CD40 pathway stimulation with anti-CD40 Ab.1.

[0167] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention.

CLAIMS

1. A method for predicting responsiveness of a subject having B-cell lymphoma to an anti-CD40 antibody treatment, comprising the steps of:

(a) measuring expression levels of RNA transcripts of marker genes in a sample comprising B lymphoma cells obtained from said subject, wherein said marker genes comprise BCL6, IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7;

(b) classifying the subject as a responsive or non-responsive subject using a K-nearest neighbors analysis based on the expression level of said marker genes in the sample from the subject and reference samples with known classes.

2. The method of claim 1, wherein the expression levels of the RNA transcripts of said marker genes are normalized.

3. The method of claim 1, wherein the reference samples are samples comprising B lymphoma cells obtained from subjects whose responsiveness to the anti-CD40 antibody treatment has been tested.

4. The method of claim 3, wherein the reference samples comprise the same type of B lymphoma cells as the sample from the subject whose responsiveness to the anti-CD40 antibody treatment is predicted.

5. The method of any one of claims 1-4, wherein the classification of the subject in step (b) is carried out by: (1) determining parameter K; (2) calculating the difference between the measured expression level of the marker genes in the sample from the subject and the expression level of the respective marker genes in each reference sample; (3) determining the nearest reference samples by selecting those samples with the smallest weighted average of the absolute differences (WAAD) between the sample from the subject and the reference sample; and (4) determining the class of the subject based on the known classes of the K-nearest reference samples.

6. The method of claim 5, wherein parameter K is 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 in the K-nearest neighbors analysis.
7. The method of any one of claims 1-6, wherein said anti-CD40 antibody treatment is a treatment with an agonist anti-CD40 antibody.
8. The method of claim 7, wherein the agonist anti-CD40 antibody stimulates CD40 and enhances the interaction between CD40 and CD40 ligand.
9. The method of claim 7, wherein the agonist anti-CD40 antibody comprises a heavy chain amino acid sequence shown in SEQ ID NO:1 and a light chain amino acid sequence shown in SEQ ID NO:2.
10. The method of claim 7, wherein the agonist anti-CD40 antibody stimulates CD40 and does not enhance or inhibits the interaction between CD40 and CD40 ligand.
11. The method of any one of claims 1-10, wherein said B cell lymphoma is diffuse large B-cell lymphoma (DLBCL).
12. The method of any one of claims 1-10, wherein said B cell lymphoma is non-Hodgkin's lymphoma.
13. The method of claim 12, wherein said non-Hodgkin's lymphoma is follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, or small lymphocytic lymphoma.
14. The method of any one of claims 1-13, wherein the sample is formalin fixed paraffin embedded biopsy sample.
15. The method of any one of claims 1-14, wherein the expression levels of the RNA transcripts of said marker genes are measured by qRT-PCR.

16. The method of any one of claims 1-14, wherein the expression levels of the RNA transcripts of said marker genes are measured by microarray.

17. A kit when used in the method of any one of the preceding claims for predicting responsiveness of a subject having B-cell lymphoma to an anti-CD40 antibody treatment, the kit comprising reagents for measuring the expression levels of the RNA transcripts of marker genes in a sample comprising B lymphoma cells from the subject, and optionally instructions for classifying the subject as a responsive or non-responsive subject using a K-nearest neighbors analysis based on the expression levels of the RNA transcripts of said marker genes in the sample from the subject and reference samples with known classes, wherein said marker genes comprise BCL6, IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7.

18. The kit of claim 17, wherein the reagents comprise at least a pair of primers and a probe for detecting the expression levels of the RNA transcripts of said marker genes by qRT-PCR.

19. The kit of claim 18, wherein said pair of primers and probe is selected from the group consisting of SEQ ID NOS:102, 103, and 104; SEQ ID NOS:108, 109 and 110; SEQ ID NOS:27, 28 and 29; SEQ ID NOS:60, 61, and 62; SEQ ID NOS:93, 94, and 95; SEQ ID NOS:24, 25, and 26; SEQ ID NOS:57, 58, and 59; SEQ ID NOS:90, 91 and 92; SEQ ID NOS:114, 115, and 116; SEQ ID NOS:126, 127, and 128; SEQ ID NOS:30, 31, and 32; SEQ ID NOS:63, 64, and 65; SEQ ID NOS:96, 97, and 98; SEQ ID NOS:12, 13, and 14; SEQ ID NOS:45, 46, and 47; SEQ ID NOS:78, 79, and 80; SEQ ID NOS:141, 142, and 143; SEQ ID NOS:150, 151, and 152; SEQ ID NOS:159, 160, and 161; SEQ ID NOS:15, 16, and 17; SEQ ID NOS:48, 49, and 50; SEQ ID NOS:81, 82, and 83; SEQ ID NOS:9, 10, and 11; SEQ ID NOS:42, 43, and 44; SEQ ID NOS:75, 76, and 77; SEQ ID NOS:6, 7, and 8; SEQ ID NOS:39, 40, and 41; SEQ ID NOS:72, 73, and 74; SEQ ID NOS:174, 175, and 176; SEQ ID NOS:180, 181, and 182; SEQ ID NOS:186, 187, and 188; SEQ ID NOS:165, 166, and 167; SEQ ID NOS:168, 169, and 170; SEQ ID NOS:171, 172, and 173; SEQ ID NOS:21, 22, and 23; SEQ ID NOS:54, 55, and 56; SEQ ID NOS:87, 88, and 89; SEQ ID NOS:129, 130, and 131; SEQ ID NOS:132, 133, and 134; SEQ ID NOS:135, 136, and 137; SEQ ID NOS:138, 139, and 140; SEQ ID NOS:147, 148, and 149; SEQ ID NOS:156, 157, and 158; SEQ ID

NOS:177, 178, and 179; SEQ ID NOS:183, 184, and 185; and SEQ ID NOS:189, 190, and 191.

20. The method of claim 1 or the kit of claim 17, substantially as hereinbefore described with reference to the examples and figures.

VNN2

LOCUS NM_004665 2034 bp mRNA linear PRI 03-SEP-2007
DEFINITION Homo sapiens vanin 2 (VNN2), transcript variant 1, mRNA.
ACCESSION NM_004665
VERSION NM_004665.2 GI:17865813

```
1 aaaccttggc catggtcact tcctcttttc caatctctgt ggcagttttt gccctaataa
61 ccctgcaggt tggtaactcag gacagtttta tagctgcagt gtatgaacat gctgtcattt
121 tgccaaataa aacagaaaca ccagtttctc aggaggatgc cttgaatctc atgaacgaga
181 atatagacat tctggagaca gcgatcaagc aggcagctga gcagggtgct cgaatcattg
241 tgactccaga agatgcactt tatggatgga aatttaccag ggaaactgtt ttcccttatc
301 tggaggatat ccagaccct caggtgaact ggattccgtg tcaagacccc cacagatttg
361 gtcacacacc agtacaagca agactcagct gcctggccaa ggacaactct atctatgtct
421 tggcaaattt gggggacaaa aagccatgta attcccgtga ctccacatgt cctcctaattg
481 gctactttca atacaatacc aatgtgggtg ataatacaga aggaaaactc gtggcacggt
541 accataagta ccacctgtac tctgagcctc agtttaatgt ccctgaaaag ccggagttgg
601 tgactttcaa caocgcattt ggaaggtttg gcattttcac gtgctttgat atattcttct
661 atgatcctgg tgttaccctg gtgaaaagatt tccatgtgga caccatactg tttcccacag
721 cttggatgaa cgttttgccc cttttgacag ctattgaatt ccattcagct tgggcaatgg
781 gaatgggagt taatcttctt gtggccaaca cacatcatgt cagcctaaat atgacaggaa
841 gtggtattta tgcaccaaag ggtcccaaag tgtatcatta tgacatgaag acagagttgg
901 gaaaacttct cctttcagag gtggattcac atcccctatc ctgcgttgcc taccacaacag
961 ctgttaattg gaatgcctac gccaccacca tcaaaccatt tccagtacag aaaaacactt
1021 tcaggggatt tatttccagg gatgggttca acttcacaga actttttgaa aatgcaggaa
1081 accttacagt ctgtcaaaaag gagctttgct gtcatttaag ctacagaatg ttacaaaaag
1141 aagagaatga agtatacggt ctaggagctt ttacaggatt acatggccga aggagaagag
1201 agtactggca ggtctgcaca atgctgaagt gcaaaaactac taatttgaca acttgtggac
1261 ggccagtaga aactgcttct acaagatttg aaatgttctc cctcagtggc acatttggaa
1321 cagagtatgt ttttctgaa gtgctactta ccgaaattca tctgtcacct ggaaaatttg
1381 aggtgctgaa agatgggctg ttggtaaaaca agaatggatc atctgggcct atactaacag
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1501 attcagcaat aacttacctg ctaatatcca tattattaat gatcatagct ttgcaaaata
1561 ttgtaatggt atagggcgct tctttatcac tcagcttctg catcatatgc ttggctgaat
1621 gtgtttatcg gcttcccaag tttactaaga aactttgaag ggctatttca gtagtataga
1681 ccagtgagtc ctaaaatattt tttctcatca ataattattt tttaagtatt atgataatgt
1741 tgtccatttt tttggctact ctgaaatggt gcagtgtgga acaatggaaa gagcctgggt
1801 gtttgggtca gataaatgaa gatcaaaactc cagctccagc ctcatattgt tgagactttg
1861 tgtgtatggg ggacttgtat gtatgggagt gaggagtttc agggccattg caaacatagc
1921 tgtgcccttg aagagaatag taatgatggg aatttagagg tttatgactg aattcccttt
1981 gacattaaaag actatttgaa ttcaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa
```

Figure 1-1

RGS13

LOCUS NM_002927 1498 bp mRNA linear PRI 24-AUG-2007
DEFINITION Homo sapiens regulator of G-protein signaling 13 (RGS13),
transcript variant 1, mRNA.
ACCESSION NM_002927
VERSION NM_002927.3 GI:21464137
KEYWORDS .
SOURCE Homo sapiens (human)

ORIGIN

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1 gaggccagag tgccatcgaa ggtaattata gagacagtaa aatcctttta ctctgggaaa
61 aataaaatgc tgggtgtctc acaaaatttc agaacctgat ttcaaacgga tcataacaaa
121 gaggatgata aatttagcat ggtggactgc tgcacaggat atatttgtca atggaatggt
181 tccacataatt ataccaccaa catgagaaaa aaatgatcat tgtttatttg aagcttgatg
241 atattctaac gctgcctttt ctcttctcat tttagagaaa aatgagcagg cggaattgtt
301 ggatttgtta gatgtgcaga gatgaatcta agaggcccc ttcaaacctt actttggagg
361 aagtattaca gtgggcccag tcttttgaaa atttaatggc tacaaaatat ggtccagtag
421 tctatgcagc atatttaaaa atggagcaca gtgacgagaa tattcaattc tggatggcat
481 gtgaaaccta taagaaaatt gcctcacggg ggagcagaat ttctagggca aagaagcttt
541 ataagattta catccagcca cagtccccta gagagattaa cattgacagt tcgacaagag
601 agactatcat caggaacatt caggaaccca ctgaaacatg ttttgagaa gctcagaaaa
661 tagtctatat gcatatggaa agggattcct accccagatt tctaaagtca gaaatgtacc
721 aaaaactttt gaaaactatg cagtccaaca acagtttctg actacaactc aaaagtttaa
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841 cagaaacaca gtacaaataa aacagaaatc aaactataag ttgactttta gttcctaaaa
901 agaaacatat ttcaaaagca atggaatcta gaattcttat aacatgaata acaaaatgta
961 cagcaagcct atgtagttca attaatatat aaggaaaagg aagggtcttc ttcattgatac
1021 aagcattata aagttttttac tgtagtagtc aattaatgga tatttcottg ttaataaaat
1081 tttgtgtcat aatttacaaa ttagttcttt aaaaattggt gttatatgaa ttgtgtttct
1141 agcatgaatg ttctatagag tactctaaat aacttgaatt tatagacaaa tgctactcac
1201 agtacaatca attgtattat accatgagaa aatcaaaaag gtgttcttca gagacatttt
1261 atctataaaa ttttcctact attatgttca ttaacaaact tctttatcac atgtatcttc
1321 tacatgtaaa acatttctga tgatttttta acaaaaaata tatgaatttc ttcatttgct
1381 cttgcatcta cattgctata aggatataaa atgtggtttc tatattttga gatgtttttt
1441 ccttacaatg tgaactcatc gtgatcttgg aaatcaataa agtcaaatat caactaaa
```

Figure 1-2

CD22

LOCUS NM_001771 3260 bp mRNA linear PRI 03-SEP-2007
 DEFINITION Homo sapiens CD22 molecule (CD22), mRNA.
 ACCESSION NM_001771
 VERSION NM_001771.1 GI:4502650
 KEYWORDS .
 SOURCE Homo sapiens (human)

ORIGIN

```

1  ccataccata  gtgaggggaag  acacgcggaa  acaggcttgc  acccagacac  gacaccatgc
61  atctcctcgg  cccctggctc  ctgctcctgg  ttctagaata  cttggctttc  tctgactcaa
121  gtaaatgggt  ttttgagcac  cctgaaaccc  tctacgcctg  ggagggggcc  tgcgtctgga
181  tccctgcac  ctacagagcc  ctgatgggtg  acctggaaag  cttcatcctg  ttccacaatc
241  ctgagtataa  caagaacacc  tcgaagtttg  atgggacaag  actctatgaa  agcacaaagg
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481  cacctcatat  ccagctccct  ccagaaatc  aagagtccca  ggaagtcact  ctgacctgct
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721  aggatgcaga  tgggaagttc  ctctccaatg  acacgggtgc  gctgaacgtg  aagcacaccc
781  cgaagtggga  gatcaaggtc  actcccagtg  atgccatagt  gagggagggg  gactctgtga
841  ccatgacctg  cgaggtcagc  agcagcaacc  cggagtacac  gacggtatcc  tggctcaagg
901  atgggacctc  gctgaagaag  cagaatacat  tcacgctaaa  cctgcgcgaa  gtgaccaagg
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1021  aagtgttctc  gcaagtgcag  tatgccccgg  aaccttccac  ggttcagatc  ctccactcac
1081  cggctgtgga  ggggaagtcaa  gtcgagtttc  tttgcatgtc  actggccaat  cctcttccaa
1141  caaattacac  gtggtaccac  aatgggaaag  aaatgcaggg  aaggacagag  gagaaagtcc
1201  acatcccaaa  gatcctcccc  tggcacgctg  ggacttattc  ctgtgtggca  gaaaacattc
1261  ttggtactgg  acagaggggc  ccgggagctg  agctggatgt  ccagtatcct  cccaagaagg
1321  tgaccacagt  gattcaaaac  cccatgccga  ttcgagaagg  agacacagtg  accctttcct
1381  gtaactacaa  ttccagtaac  cccagtgtta  cccggtatga  atggaaaccc  catggcgctc
1441  gggaggagcc  atcgcttggg  gtgctgaaga  tccaaaacgt  tggctgggac  aacacaacca
1501  tcgcctgcgc  acgttgtaat  agttggtgct  cgtgggcctc  cctgtgcgcc  ctgaatgtcc
1561  agtatcccc  ccgagacgtg  aggtccgga  aaatcaagcc  cctttccgag  attcactctg
1621  gaaactcggg  cagcctccaa  tgtacttct  caagcagcca  ccccaaagaa  gtccagttct
1681  tctgggagaa  aaatggcagg  cttctgggga  aagaaagcca  gctgaatttt  gactccatct
1741  cccagaaga  tgctgggagt  tacagctgct  gggatgaaca  ctccatagga  cagacagcgt
1801  ccaaggcctg  gacacttgaa  gtgctgtatg  caccagggag  gctgcgtgtg  tccatgagcc
1861  cgggggacca  agtgatggag  ggaagagtg  caaccctgac  ctgtgagagt  gacgccaacc
1921  ctcccgctc  ccactacacc  tggtttgact  ggaataacca  aagcctcccc  caccacagcc
1981  agaagctgag  attggagccg  gtgaaggctc  agcactcggg  tgccactagg  tgccagggga
2041  ccaacagtg  gggcaagggc  cgttcgcctc  tcagcacctc  tactgtctac  tatagccggg
2101  agaccatcgg  caggcgagtg  gctgtgggac  tcgggtcctg  cctcgccatc  ctcatcctgg
2161  caatctgtgg  gctcaagctc  cagcgacgtt  ggaagaggac  acagagccag  caggggcttc
2221  aggagaattc  cagcggccag  agcttctttg  tgaggaataa  aaagggttaga  agggccccc
2281  tctctgaagg  ccccaactcc  ctgggatgct  acaatccaat  gatggaagat  ggcattagct
2341  acaccacct  gcgctttccc  gagatgaaca  taccacgaac  tggagatgca  gagtccctcag

```

Figure 1-3

```
2401 agatgcagag acctccccgg acctgcgatg acacgggtcac ttattcagca ttgcacaagc
2461 gccaagtggg cgactatgag aacgtcattc cagatTTttcc agaagatgag gggattcatt
2521 actcagagct gatccagttt ggggtcgggg agcggcctca ggcacaagaa aatgtggact
2581 atgtgatcct caaacattga cactggatgg gctgcagcag aggcactggg ggcagcgggg
2641 gccagggaag tccccgagtt tccccagaca ccgccacatg gcttctctct gcgtgcatgt
2701 gcgcacacac acacacacac gcacacacac acacacacac tcaactgcgga gaaccttgtg
2761 cctggctcag agccagtctt tttggtgagg gtaaccccaa acctccaaaa ctctgcccc
2821 tgttctcttc cactctcctt gctaccaga aatcatctaa atacctgcc tgacatgcac
2881 acctccctg cccaccagc ccactggcca tctccaccg gagctgctgt gtcctctgga
2941 tctgctcgtc attttccttc cttctccat ctctctggcc ctctacctt gatctgacat
3001 cccactcac gaatattatg ccagtttct gcctctgagg gaaagcccag aaaaggacag
3061 aaacgaagta gaaaggggcc cagtcctggc ctggcttctc ctttggaggt gaggcattgc
3121 acggggagac gtacgtatca gcggccctt gactctgggg actccgggtt tgagatggac
3181 aactgggtgt ggattaacct gccagggaga cagagctcac aataaaaatg gctcagatgc
3241 cacttcaaag aaaaaaaaaa
```

Figure 1-4

CD40

LOCUS NM_001250 1616 bp mRNA linear PRI 30-SEP-2007
 DEFINITION Homo sapiens CD40 molecule, TNF receptor superfamily member 5 (CD40), transcript variant 1, mRNA.
 ACCESSION NM_001250
 VERSION NM_001250.4 GI:91105420
 KEYWORDS .
 SOURCE Homo sapiens (human)

ORIGIN

```

1  gccaaaggctg gggcagggga gtcagcagag gcctcgctcg ggcgcccagt ggtcctgccg
61  cctgggtctca cctcgctatg gttcgtctgc ctctgcagtg cgtcctcttg ggctgcttgc
121  tgaccgctgt ccatccagaa ccacccactg catgcagaga aaaacagtac ctaataaaca
181  gtcagtgtctg ttctttgtgc cagccaggac agaaactggg gagtgactgc acagagttca
241  ctgaaacgga atgccttcct tgcggtgaaa gcgaattcct agacacctgg aacagagaga
301  cacctgcca ccagcacaaa tactgcgacc ccaacctagg gcttcggggtc cagcagaagg
361  gcacctcaga aacagacacc atctgcacct gtgaagaagg ctggcactgt acgagtgagg
421  cctgtgagag ctgtgtcctg caccgctcat gctcgcccgg ctttgggggtc aagcagattg
481  ctacaggggt ttctgatacc atctgcgagc cctgcccagt cggcttcttc tccaatgtgt
541  catctgcttt cgaaaaatgt cacccttgga caagctgtga gaccaaagac ctggttgtgc
601  aacaggcagg cacaacaag actgatgttg tctgtggtcc ccaggatcgg ctgagagccc
661  tgggtggtgat ccccatcatc ttcgggatcc tgtttgccat cctcttggtg ctggtcttta
721  tcaaaaagggt ggccaagaag ccaaccaata agggccccca cccaagcag gaaccccagg
781  agatcaatth tcccgcgat cttcctggct ccaacactgc tgctccagtg caggagactt
841  tacatggatg ccaaccggtc acccaggagg atggcaaaga gagtcgcata tcagtgcagg
901  agagacagtg aggctgcacc caccaggagg tgtggccacg tgggcaaaca ggcagttggc
961  cagagagcct ggtgctgctg ctgctgtggc gtgagggtga ggggctggca ctgactgggc
1021  atagctcccc gcttctgcct gcaccctgc agtttgagac aggagacctg gcaactggatg
1081  cagaaacagt tcaccttgaa gaacctctca cttcaccctg gagcccatcc agtctcccaa
1141  cttgtattaa agacagaggc agaagtttgg tgggtggtgg gtgggggtat ggtttagtaa
1201  tatccaccag accttccgat ccagcagttt ggtgcccaga gaggcatcat ggtggcttcc
1261  ctgcgcccag gaagccatat acacagatgc ccattgcagc attgtttgtg atagtgaaca
1321  actggaagct gcttaactgt ccatcagcag gagactggct aaataaaatt agaatatatt
1381  tatacaacag aatctcaaaa aactgttgta gtaaggaaaa aaaggcatgc tgctgaatga
1441  tgggtatgga acttttttaa aaagtacatg cttttatgta tgtatattgc ctatggatat
1501  atgtataaat acaatatgca tcatatattg atataacaag ggttctggaa ggggtacacag
1561  aaaaccacac gctcgaagag tgggtgacgtc tggggtgggg aagaagggtc tggggg

```

Figure 1-5

IFITM1

LOCUS NM_003641 733 bp mRNA linear PRI 03-SEP-2007
DEFINITION Homo sapiens interferon induced transmembrane protein 1 (9-27)
(IFITM1), mRNA.
ACCESSION NM_003641
VERSION NM_003641.3 GI:150010588
KEYWORDS .
SOURCE Homo sapiens (human)

ORIGIN

```
1 aaacagcagg aaatagaaac ttaagagaaa tacacacttc tgagaaactg aaacgacagg
61 ggaaaggagg tctcactgag caccgtccca gcatccggac accacagcgg cccttcgctc
121 cacgcagaaa accacacttc tcaaaccttc actcaacact tccttcccca aagccagaag
181 atgcacaagg aggaacatga ggtggctgtg ctggggggcac cccccagcac catccttcca
241 aggtccaccg tgatcaacat ccacagcgag acctccgtgc ccgaccatgt cgtctggtcc
301 ctgttcaaca ccctcttctt gaactggtgc tgtctgggct tcatagcatt cgcctactcc
361 gtgaagtcta gggacaggaa gatggttggc gacgtgaccg gggcccaggc ctatgcctcc
421 accgccaagt gcctgaacat ctgggccctg attctgggca tcctcatgac cattggattc
481 atcctgttac tgggtattcg ctctgtgaca gtctaccata ttatgttaca gataatacag
541 gaaaaacggg gttactagta gccgcccata gcctgcaacc tttgcactcc actgtgcaat
601 gctggccctg cacgctgggg ctgttgcccc tgcccccttg gtcttgcccc tagatacagc
661 agtttatacc cacacacctg tctacagtgt cattcaataa agtgcacgtg cttgtgaaaa
721 aaaaaaaaaa aaa
```

Figure 1-6

BCL6

LOCUS NM_001706 3537 bp mRNA linear PRI 30-SEP-2007
 DEFINITION Homo sapiens B-cell CLL/lymphoma 6 (zinc finger protein 51)
 (BCL6), transcript variant 1, mRNA.
 ACCESSION NM_001706
 VERSION NM_001706.2 GI:21040323
 KEYWORDS .
 SOURCE Homo sapiens (human)

ORIGIN

```

1  ggccctcgga ggcctcgaacc ggaacctcca aatccgagac gctctgctta tgaggacctc
61  gaaatatgcc ggccagtgaa aaaaatttgt ggctttgagg gcttttggtt ggccaggggc
121 agtaaaaatc tcggagagct gacaccaagt cctcccctgc cacgtagcag tggtaaagtc
181 cgaagctcaa attccgagaa ttgagctctg ttgattctta gaactggggt tcttagaagt
241 ggtgatgcaa gaagtttcta ggaaaggccg gacaccaggt tttgagcaaa attttgact
301 gtgaagcaag gcattgggtga agacaaaatg gcctcgcccg ctgacagctg tatccagttc
361 acccgccatg ccagtgatgt tcttctcaac cttaatcgtc tccggagtcg agacatcttg
421 actgatgttg tcattgttgt gagccgtgag cagtttagag ccataaaac ggtcctcatg
481 gcctgcagtg gcctgttcta tagcatcttt acagaccagt tgaaatgcaa ccttagtgtg
541 atcaatctag atcctgagat caaccctgag ggattctgca tcctcctgga cttcatgtac
601 acatctcggc tcaatttgcg ggagggcaac atcatggctg tgatggccac ggctatgtac
661 ctgcagatgg agcatgttgt ggacacttgc cggaggttta ttaaggccag tgaagcagag
721 atggtttctg ccatcaagcc tcctcgtgaa gagttcctca acagccggat gctgatgccc
781 caagacatca tggcctatcg gggcgtgag gtgggtggaga acaacctgcc actgaggagc
841 gccctgggtg gtgagagcag agcctttgcc cccagccctgt acagtggcct gtccacaccg
901 ccagcctctt attccatgta cagccaacct cctgtcagca gcctcctctt ctccgatgag
961 gagtttcggg atgtccggat gcctgtggcc aacccttcc ccaaggagcg ggcactccca
1021 tgtgatagtg ccaggccagt ccctggtgag tacagccggc cgactttgga ggtgtcccc
1081 aatgtgtgcc acagcaatat ctattcacc aaggaaacaa tcccagaaga ggcacgaagt
1141 gatatgact acagtgtggc tgagggcctc aaacctgctg cccctcagc ccgaaatgcc
1201 ccctacttcc cttgtgacaa ggccagcaaa gaagaagaga gaccctctc ggaagatgag
1261 attgccctgc atttcgagcc cccaatgca cccctgaacc ggaagggtct ggtagtcca
1321 cagagcccc agaaatctga ctgccagccc aactcgccca cagagtctg cagcagtaag
1381 aatgcctgca tcctccaggc ttctggctcc cctccagcca agagccccac tgaccccaaa
1441 gcctgcaact ggaagaaata caagttcatc gtgctcaaca gcctcaacca gaatgccaaa
1501 ccagaggggc ctgagcaggc tgagctgggc cgcctttccc cagcagccta cacggcccca
1561 cctgcctgcc agccacccat ggagcctgag aaccttgacc tccagtcccc aaccaagctg
1621 agtgccagcg gggaggactc caccatccca caagccagcc ggctcaataa catcgtaaac
1681 aggtccatga cgggctctcc ccgcagcagc agcgagagcc actcaccact ctacatgcac
1741 ccccggaagt gcacgtcctg cggctctcag tccccacagc atgcagagat gtgcctccac
1801 accgtgggcc ccacgttccc tgaggagatg ggagagaccc agtctgagta ctcagattct
1861 agctgtgaga acggggcctt cttctgcaat gactgtgact gccgcttctc tgaggaggcc
1921 tactcaaga ggcacacgct gcagacccac agtgacaaac cctacaagtg tgaccgctgc
1981 caggcctct tccgctacaa gggcaacctc gccagccaca agaccgtcca taccggtgag
2041 aaacctatc gttgcaacat ctgtgggggc cagttcaacc ggccagccaa cctgaaaacc
2101 cacactcgaa ttcactctgg agagaagccc tacaaatgag aaacctgagg agccagattt
2161 gtacagggtg ccacacctcg tgcccatgtg cttatccaca ctggtgagaa gccctatccc
2221 tgtgaaatct gtggcaccgc ttccggcac cttcagactc tgaagagcca cctgcgaatc
2281 cacacaggag agaaacctta ccattgtgag aagtgttaacc tgcatttccg tcacaaaagc
2341 cagctgcgac ttcacttgcg ccagaagcat ggcgccatca ccaacaccaa ggtgcaatac

```

Figure 1-7

```
2401 cgcgtgtcag ccactgacct gcctccggag ctccccaag cctgctgaag catggagtgt
2461 tgatgctttc gtctccagcc ccttctcaga atctacccaa aggatactgt aacactttac
2521 aatgttcac ccatgatgta gtgcctcttt catccactag tgcaaatcat agctgggggt
2581 tgggggtggt ggggggtcggg gcctggggga ctgggagccg cagcagctcc ccctcccca
2641 ctgccataaa acattaagaa aatcatattg cttcttctcc tatgtgtaag gtgaaccatg
2701 tcagcaaaaa gcaaaatcat tttatatgtc aaagcagggg agtatgcaaa agttctgact
2761 tgactttagt ctgcaaaatg aggaatgtat atgttttgtg ggaacagatg tttcttttgt
2821 atgtaaatgt gcattctttt aaaagacaag acttcagtat gttgtcaaag agagggcttt
2881 aattttttta accaaagggtg aaggaatata tggcagagtt gtaaataatat aaatatatat
2941 atatataaaa taaatatata taaacctaac aaagatatat taaaaatata aaactgcgtt
3001 aaaggctcga ttttgtatct gcaggcagac acggatctga gaatctttat tgagaaagag
3061 cacttaagag aatattttta gtattgcac tgtataagta agaaaatatt ttgtctaaaa
3121 tgcctcagtg tatttgtatt tttttgcaag tgaaggttta caatttacia agtgtgtatt
3181 aaaaaaaaca aaaagaacaa aaaaatctgc agaaggaaaa atgtgtaatt ttgttctagt
3241 tttcagtttg tatatacccg tacaacgtgt cctcacgggtg ccttttttca cggaagtttt
3301 caatgatggg cgagcgtgca ccatcccttt ttgaagtgtg ggcagacaca gggacttgaa
3361 gttgttacta actaaactct ctttgggaat gtttgtctca tccattctg cgtcatgctt
3421 gtgttataac tactccggag acagggtttg gctgtgtcta aactgcatta ccgcgttgta
3481 aaatatagct gtacaaatat aagaataaaa tggtgaaaag tcaaaactgga aaaaaaa
```

Figure 1-8

EPDR1

LOCUS NM_017549 2613 bp mRNA linear PRI 26-JUN-2007
 DEFINITION Homo sapiens endodymin related protein 1 (zebrafish) (EPDR1), mRNA.
 ACCESSION NM_017549
 VERSION NM_017549.3 GI:116008437
 SOURCE Homo sapiens (human)

ORIGIN

```

1  tccccctct taaaacacga tgcctcccag gatgctagt gcaccactgc cactgcattt
61  cctgttggca gcagtgagca gtgaaaaccg aagcggcaga aggcagtggc agcaggcagt
121  ggcagcaggc agtggcccag gcagaaatag ctcccgcgcg attcactgga gccttccccg
181  ggccctgggt ccggctaccg ggactcgcgc gtccggatct caaaagcggc agaggccacc
241  gaaggacacg gaagcacttt ggtccagacc aactcccgg cacagtgcgg aaagagccgg
301  cgggagccac tctgatcccg gacgcctcag cgcccccttg ggcttgggct tgccctcggg
361  ccggggaagg ctgaccgcga tgccaggacg cgctcccctc cgcaccgtcc cgggcgccct
421  ggggtgcctg ctgctgggcg gcctctgggc ctggaccctg tgcggcctgt gcagcctggg
481  ggcgtgggga gccccgcgcc cgtgccaggc gccgcagcag tgggaggggc gccaggttat
541  gtaccagcaa agtagcgggc gcaacagccg cgccctgctc tctacgacg ggctcaacca
601  gcgctgcgcy gtgctggacg agaggaaagg gctgatcccc tgcaagagat tatttgaata
661  tattttgctg tataaggatg gagtgatgtt tcagattgac caagccaacca agcagtgtct
721  aaagatgacc ctgacacagc cctgggatcc tcttgacatt cctcaaaact ccaccttga
781  agaccagtac tccatcgggg ggctcagga gcagatcacc gtccaggagt ggtcggacag
841  aaagtcagct agatcctatg aaacctggat tggcatctat acagtcaagg attgctatcc
901  tgtccaggaa acctttacca taaactacag tgtgatattg tctacgcggt tttttgacat
961  ccagctgggt attaaagacc cctcgggtgt taccctcca agcacgtgcc agatggccca
1021  actggagaag atgagcgaag actgctcctg gtgagcctgt gcatagggaa gcggcagcat
1081  cggatgtcag cccctgcgcy cccagctgg agatggatat gagactagtc aagatgtgaa
1141  tgctaattgg agagaaatat aatttttagga agatgcacat tgatgtgggg ttttgatgtg
1201  tctgattttg actactcaag ctctgtttac agaagaaaat tgaatggcga ggggtgtggc
1261  atatgaactg actagatggc taatatggac actttgggta tttctaagtc ctgttcaggg
1321  ctggttttct gcatgcacgg gtatacacat aatgcagtgc catgcacata ggaagggtc
1381  agtaagagaa gtttgccttg gcagcaagta tttattgttg acattattca gaattagtga
1441  taataaaaaa cagagtgatt ttggtcaatt ttattattaa ttcttaaatt ccctgcagag
1501  aatgccccct ttattgctgc accagggttg gcattgctcc cactgagccc tactccccc
1561  tgtccctgca ctcccttggg tgccaaaaaa atgataactt aaatcccttc cagacttaag
1621  aattttatgg catggcccaa ttgatataaa catttagaag gaaatgaaaa gctaaaatag
1681  gaagtaatta ttcctctaaa gaaacatttt gagcaaggca gttagagaaa tcctaattgtc
1741  tacactggca tagcacgagc catgtaagct tctttttttt ctatgcaaga gtattgatgt
1801  atgtgctgaa tcttcacaga cttgtcaata cacaggcagt attctaaaat agcactgaac
1861  agggagtcat gagactattg tctcctaaac ccaggactag agttccctcg tactgtcact
1921  cctttgggtc ttaaattgcac tggccttgcc cgcactttgg ccttctaga acactgcttc
1981  ataacctctc tgtctgactt ctgcatctcc ttccagggtc gctcattcac aagagttgct
2041  cccaagcctg gatgagttgc acctgcatc ttgagcatgc atttctcaca ataattatta
2101  agctgtgtga taatttctgc tttcaggaca ctcatccatt atcttggctg tgagctcctt
2161  gggtaggggt acctgtatg tttactttta tatccctagc acaaagcaag tgccctggcac
2221  atagtcagtg ccctaagtat tcgtagagtg aagaatgccg gcctctcttg tccctggttt
2281  ccttatgtgt tgaatgtggt tgagtttgtc cattgctagg gagagacttc cagtaataaa
2341  atttactatt ctagatgctt ctactgttat gttttatctg cccattttatc tttcttagtt
2401  accaggagaa atgtgtgaca cctatattat aatgaaaaca atctcattac ttatagttta
2461  tctatattaa acaaatttaa ttgcatttta aagcattctt tgatactgtt gcttttgcaa
2521  taaatatgga taatcttggg tataagggag ttaaaacaat gctgtaataa ataaagtgtc
2581  tcatgtgatc aaaatcaaaa aaaaaaaaaa aaa

```

Figure 1-9

IGF1R

LOCUS NM_000875 11242 bp mRNA linear PRI 22-OCT-2007
 DEFINITION Homo sapiens insulin-like growth factor 1 receptor (IGF1R), mRNA.
 ACCESSION NM_000875 NM_015883
 VERSION NM_000875.3 GI:119220593
 KEYWORDS .
 SOURCE Homo sapiens (human)

ORIGIN

```

1  tttttttttt ttttttttga gaaaggggaa tttcatccca aataaaagga atgaagtctg
61  gctccggagg aggggtcccc acctcgtctg gggggctcct gtttctctcc gccgcgctct
121 cgctctggcc gacgagtggg gaaatctgcg ggccaggcat cgacatccgc aacgactatc
181 agcagctgaa ggcctggag aactgcacgg tgatcgaggg ctacctccac atcctgctca
241 tctccaaggc cgaggactac cgcagctacc gcttccccaa gctcacggtc attaccgagt
301 acttgctgct gttccgagtg gctggcctcg agagcctcgg agacctcttc cccaacctca
361 cggatcatccg cggctggaaa ctctcttaca actacgccct ggatcatctc gagatgacca
421 atctcaagga tattgggctt tacaacctga ggaacattac tcggggggcc atcaggattg
481 agaaaaatgc tgacctctgt tacctctcca ctgtggactg gtccctgata ctggatgcgg
541 tgtccaataa ctacattgtg gggaataagc ccccaaagga atgtggggac ctgtgtccag
601 ggaccatgga ggagaagccg atgtgtgaga agaccacat caacaatgag tacaactacc
661 gctgctggac cacaaccgc tgccagaaaa tgtgcccaag cacgtgtggg aagcgggcgt
721 gcaccgagaa caatgagtgc tgccaccccg agtgccctggg cagctgcagc ggcctgaca
781 acgacacggc ctgtgtagct tgccgccact actactatgc cgggtgtctg gtgcctgcct
841 gcccgcccaa cacctacagg tttgagggct ggcgctgtgt ggaccgtgac ttctgcgcca
901 acatcctcag cgcgagagc agcgactccg aggggtttgt gatccacgac ggcgagtgca
961 tgcaggagtg cccctcgggc ttcatccgca acggcagcca gagcatgtac tgcattccct
1021 gtgaagggtc ttgcccgaag gtctgtgagg aagaaaagaa aacaaagacc attgattctg
1081 ttacttctgc tcagatgtc caaggatgca ccattctcaa gggcaatttg ctcatataca
1141 tccgacgggg gaataacatt gcttcagagc tggagaactt catggggctc atcgaggtgg
1201 tgacgggcta cgtgaagatc cgcattcttc atgccttggg ctcttgttcc ttctaaaaaa
1261 accttcgcct cactcctagga gaggagcagc tagaagggaa ttactccttc tacgtcctcg
1321 acaaccagaa cttgcagcaa ctgtgggact gggaccaccg caacctgacc atcaaagcag
1381 ggaaaatgta ctttgctttc aatcccaaat tatgtgtttc cgaaatttac cgcattggag
1441 aagtgcgggg gactaaaggg cgccaaagca aaggggacat aaacaccagg aacaacgggg
1501 agagagcctc ctgtgaaagt gacgtcctgc atttcacctc caccaccacg tcgaagaatc
1561 gcatcatcat aacctggcac cggtagccgc cccctgacta cagggatctc atcagcttca
1621 ccgtttacta caaggaagca ccctttaaga atgtcacaga gtatgatggg caggatgcct
1681 gcggctccaa cagctggaac atggtggacg tggacctccc gcccaacaag gacgtggagc
1741 ccgcatctt actacatggg ctgaagccct ggactcagta cgcggtttac gtcaaggctg
1801 tgacctcac catggtggag aacgaccata tccgtggggc caagagttag atcttgtaca
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2041 ccaaagacaa aatccccatc aggaagtatg ccgacggcac catcgacatt gaggaggtca
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2161 aaactgaagc cgagaagcag gccgagaagg aggaggctga ataccgcaaa gtctttgaga
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2281 aagtggccaa caccaccatg tccagccgaa gcaggaacac cacggccgca gacacctaca
2341 acataccgga cccggaagag ctggagacag agtacccttt ctttgagagc agagtggata
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Figure 1-10

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Figure 1-11

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Figure 1-12

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11221 aaataaaata attctgtatg ca
```

Figure 1-13

BTG2

LOCUS NM_006763 2718 bp mRNA linear PRI 25-SEP-2007
 DEFINITION Homo sapiens BTG family, member 2 (BTG2), mRNA.
 ACCESSION NM_006763
 VERSION NM_006763.2 GI:28872718
 KEYWORDS .
 SOURCE Homo sapiens (human)

ORIGIN

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241  aaaagccgtc caagggctcc ggctaccgct gcattcgcac caaccacaag atggaccca
301  tcatcagcag ggtggccagc cagatcggac tcagccagcc ccagctgcac cagctgctgc
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2341  cccaagagct aattttctgg tttgtgggtt gaaacaaagc tgtgaatcac tgcaggctgt
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Figure 1-14

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2581 tgtttgtaag ctattctgac agaaaagaca aaggttacta attgtatgat agtgttttta
2641 tatggaagaa tgtacagctt atggacaaat gtacaccttt ttgttacttt aataaaaatg
2701 tagtaggata aaaaaaaaa
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Figure 1-15

LMO2

LOCUS NM_005574 2304 bp mRNA linear PRI 30-SEP-2007
DEFINITION Homo sapiens LIM domain only 2 (rhombotin-like 1) (LMO2), mRNA.
ACCESSION NM_005574
VERSION NM_005574.2 GI:6633806
KEYWORDS .
SOURCE Homo sapiens (human)

ORIGIN

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781 gagccggcga cagcgcgcga gagggaccgg gcggtggcgg cggcgggacc gggatggaag
841 ggagcgcggt gactgtcctt gagcgcggag gggcgagctc gccggcggag gccgagcaag
901 cggaggcagg agcggcggcg acggcggcgg cggcggcggc gcccgagcac ccgagggggt
961 ccgagccccg gcagccggcc agccccgcgc cacaaaggga gcgcccccg cccccggcac
1021 cccgcctccc tccccaatgt cctcggccat cgaaaggaa agcctggacc cttcagagga
1081 accagtggat gaggtgctgc agatcccccc atccctgctg acatgcggcg gctgccagca
1141 gaacatcggg gaccgctact tcctgaaggc catcgaccag tactggcacg aggactgcct
1201 gagctgcgac ctctgtggct gccggctggg tgaggtgggg cggcgccctc actacaaact
1261 gggccggaag ctctgccgga gagaactatc caggcttttt gggcaagaag gtctctgcgc
1321 atcctgtgac aagcggattc gtgcctatga gatgacaatg cgggtgaaag acaaagtgtg
1381 tcacctggaa tgtttcaagt gcgccgcctg tcagaagcat ttctgtgtag gtgacagata
1441 cctcctcatc aactctgaca tagtgtgcga acaggacatc tacgagtggg ctaagatcaa
1501 tgggatgata taggcccag tcccggggca tctttgggga ggtgttcaact gaagacgccg
1561 tctccatggc atcttcgtct tcaactcttag gcactttggg ggtttgaggg tggggtaagg
1621 gatttccttag gggatggtag acctttattg ggtatcaaga catagcatcc aagtggcata
1681 attcaggggc tgacacttca aggtgacaga aggaccagcc cttgagggag aacttatggc
1741 cacagcccat ccatagtaac tgacatgatt agcagaagaa aggaacattt aggggcaagc
1801 aggcgctgtg ctatcatgat ggaatttcat atctacagat agagagttgt tgtgtacaga
1861 cttgttgtga ctttgacgct tgcgaactag agatgtgcaa ttgatttctt ttcttcctgg
1921 ctttttaact cccctgtttc aatcactgtc ctccacacaa ggaaggaca gaaaggagag
1981 tggccattct ttttttcttg gcccccttcc caaggcctta agctttggac ccaagggaaa
2041 actgcatgga gacgcatttc ggttgagaat ggaaaccaca acttttaacc aaacaattat
2101 ttaaagcaat gctgatgaat cactgttttt agacaccttc attttgaggg gaggagtcc
2161 acagattggt tctatacaaa tataaatctt aaaaagttgt tcaactattt tattatccta
2221 gattatatca aagtatttgt cgtgtgtaga aaaaaaaac agctctgcag gcttaataaa
2281 aatgacagac tgaaaaaaaa aaaa
```

Figure 1-16

CD79B

LOCUS NM_000626 1300 bp mRNA linear PRI 21-SEP-2008
DEFINITION Homo sapiens CD79b molecule, immunoglobulin-associated beta
(CD79B), transcript variant 1, mRNA.
ACCESSION NM_000626
VERSION NM_000626.2 GI:90193589

```
1 ctgcagccgg tgcagttaca cgttttcttc caaggagcct cggacgttgt cacggggttg
61 gggtcgggga cagagcgggtg accatggcca ggctggcggt gtctcctgtg cccagccact
121 ggatggtggc gttgctgctg ctgctctcag ctgagccagt accagcagcc agatcggagg
181 accgtaccg gaatcccaaa ggtagtgctt gttcgcggat ctggcagagc ccacgtttca
241 tagccaggaa acggggcctt acggtgaaaa tgcactgcta catgaacagc gcctccggca
301 atgtgagctg gctctggaag caggagatgg acgagaatcc ccagcagctg aagctggaaa
361 agggccgcat ggaagagtcc cagaacgaat ctctcgccac cctcaccatc caaggcatcc
421 ggtttgagga caatggcatc tacttctgtc agcagaagtg caacaacacc tcggaggtct
481 accagggctg cggcacagag ctgcgagtca tgggattcag caccttggca cagctgaagc
541 agaggaacac gctgaaggat ggtatcatca tgatccagac gctgctgac atcctcttca
601 tcatcgtgcc tatcttctg ctgctggaca aggatgacag caaggctggc atggaggaag
661 atcacacctc cgagggcctg gacattgacc agacagccac ctatgaggac atagtacgc
721 tgcggacagg ggaagtgaag tggctctgtg gtgagcacc aggccaggag tgagagccag
781 gtcgccccat gacctgggtg caggctccct ggcctcagt actgcttcgg agctgcctgg
841 ctcatggccc aacccttttc ctggaccccc cagctggcct ctgaagctgg cccaccagag
901 ctgccatttg tctccagccc ctggtcccca gctcttgcca aagggcctgg agtagaagga
961 caacagggca gcaacttggg gggagtcttc tggggatgga cgggacccag ccttctgggg
1021 gtgctatgag gtgatccgtc cccacacatg ggatggggga ggcagagact ggtccagagc
1081 ccgcaaatgg actcggagcc gagggcctcc cagcagagct tgggaagggc catggacca
1141 actgggcccc agaagagcca caggaacatc attcctctcc cgcaaccact cccacccag
1201 ggaggccctg gcctccagt ccttcccccg tggaaataaac ggtgtgtcct gagaaaccac
1261 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa
```

Figure 1-17

CD44

LOCUS NM_000610 5748 bp mRNA linear PRI 23-OCT-2008
 DEFINITION Homo sapiens CD44 molecule (Indian blood group) (CD44),
 transcript variant 1, mRNA.
 ACCESSION NM_000610
 VERSION NM_000610.3 GI:48255934

```

1  gagaagaaag ccagtgcgtc tctgggcgca ggggccagtg gggctcggag gcacaggcac
61  cccgcgacac tccaggttcc ccgacccacg tccctggcag ccccgattat ttacagcctc
121 agcagagcac ggggcggggg cagagggggc cgcccgggag ggctgctact tcttaaaacc
181 tctgcgggct gcttagtcac agccccctt gcttgggtgt gtccttgcgt cgctccctcc
241 ctccgtctta ggtcactgtt ttcaacctcg aataaaaact gcagccaact tccgaggcag
301 cctcattgcc cagcggaccc cagcctctgc caggttcggg ccgccatcct cgtcccgtcc
361 tccgccggcc cctgccccgc gccagggat cctccagctc ctttcgcccg cgccctccgt
421 tcgctccgga caccatggac aagttttggt ggcacgcagc ctggggactc tgccctcgtg
481 cgctgagcct ggcgagatc gatttgaata taacctgccg ctttgcagggt gtattccacg
541 tggagaaaaa tggtcgctac agcatctctc ggacggaggc cgctgacctc tgcaaggctt
601 tcaatagcac cttgcccaca atggcccaga tggagaaagc tctgagcatt ggatttgaga
661 cctgcaggta tgggttcata gaaggcgacg tgggtattcc ccgcatccac cccaactcca
721 tctgtgcagc aaacaacaca ggggtgtaca tcctcacatc caacacctcc cagtatgaca
781 catattgctt caatgcttca gctccacctg aagaagattg tacatcagtc acagacctgc
841 ccaatgcctt tgatggacca attaccataa ctattgttaa ccgtgatggc acccgctatg
901 tccagaaagg agaatacaga acgaatcctg aagacatcta cccagcaaac cctactgatg
961 atgacgtgag cagcggctcc tccagtgaag ggagcagcac ttcaggagggt tacatctttt
1021 acaccttttc tactgtacac cccatcccag acgaagacag tccctggatc accgacagca
1081 cagacagaat ccttgcctacc actttgatga gcactagtgc tacagcaact gagacagcaa
1141 ccaagaggga agaaacctgg gattggtttt catggttggt tctaccatca gagtcaaaga
1201 atcatcttca cacaacaaca caaatggctg gtacgtcttc aaataccatc tcagcagggt
1261 gggagccaaa tgaagaaaat gaagatgaag gagacagaca cctcagtttt tctggatcag
1321 gcattgatga tgatgaagat tttatctcca gcaccatttc aaccacacca cgggcttttg
1381 accacacaaa acagaaccag gactggaccc agtggaaacc aagccattca aatccggaag
1441 tgctacttca gacaaccaca aggatgactg atgtagacag aaatggcacc actgcttatg
1501 aaggaaaactg gaaccacaga gcacaccctc ccctcattca ccatgagcat catgaggaag
1561 aagagacccc acattctaca agcacaatcc aggcaactcc tagtagtaca acggaagaaa
1621 cagctaccca gaaggaacag tggtttgcca acagatggca tgagggatat cgccaaacac
1681 ccaaagaaga ctcccattcg acaacaggga cagctgcagc ctacagctcat accagccatc
1741 caatgcaagg aaggacaaca ccaagcccag aggacagttc ctggactgat ttcttcaacc
1801 caatctcaca ccccatggga cgaggtcatc aagcaggaag aaggatggat atggactcca
1861 gtcatagtat aacgcttcag cctactgcaa atccaaacac aggtttgggt gaagatttgg
1921 acaggacagg acctctttca atgacaacgc agcagagtaa ttctcagagc ttctctacat
1981 cacatgaagg cttggaagaa gataaagacc atccaacaac ttctactctg acatcaagca
2041 ataggaatga tgtcacaggt ggaagaagag acccaaatca ttctgaaggc tcaactactt
2101 tactggaagg ttatacctct cattacccac acacgaagga aagcaggacc ttcaccccag
2161 tgacctcagc taagactggg tcctttggag ttactgcagt tactgttggg gattccaact
2221 ctaatgtcaa tcgttcctta tcaggagacc aagacacatt ccaccccagt ggggggtccc
2281 ataccactca tggatctgaa tcagatggac actcacatgg gagtcaagaa ggtggagcaa
2341 acacaacctc tggctctata aggacacccc aaattccaga atggctgata atcttggcat
2401 ccctcttggc cttggctttg attcttgcag tttgcattgc agtcaacagt cgaagaaggt
2461 gtgggcagaa gaaaaagcta gtgatcaaca gtggcaatgg agctgtggag gacagaaagc
2521 caagtggact caacggagag gccagcaagt ctcaggaaat ggtgcatttg gtgaacaagg
2581 agtctcaga aactccagac cagtttatga cagctgatga gacaaggaac ctgcagaatg
2641 tggacatgaa gattggggtg taacacctac accattatct tggaaagaaa caaccgttgg

```

Figure 1-18

2701 aaacataacc attacagggg gctggggacac ttaacagatg caatgtgcta ctgattgttt
2761 cattgcgaat ctttttttagc ataaaaatttt ctactctttt tgttttttgt gttttgttct
2821 ttaaaagtcag gtccaatttg taaaaacagc attgctttct gaaattaggg cccaattaat
2881 aatcagcaag aatttgatcg ttccagttcc cacttgaggg cctttcatcc ctcggtgtg
2941 ctatggatgg cttctaacaa aaactacaca tatgtattcc tgatcgccaa cctttcccc
3001 accagctaag gacattttccc agggttaata gggcctggtc cctgggagga aatttgaatg
3061 ggtccatttt gcccttccat agcctaatac ctgggcattg ctttccactg aggttggggg
3121 ttggggtgta ctagttaacac atcttcaaca gacccctct agaaattttt cagatgcttc
3181 tgggagacac ccaaagggtg aagctattta tctgtagtaa actattttatc tgtgtttttg
3241 aaatattaaa ccctggatca gtccctttgat cagtataatt ttttaaagtt actttgtcag
3301 aggcacaaaa ggggtttaaac tgattcataa taaatatctg tacttcttcg atcttcacct
3361 tttgtgctgt gattcttcag tttctaaacc agcactgtct gggtcctac aatgtatcag
3421 gaagagctga gaatggtaag gagactcttc taagtcttca tctcagagac cctgagttcc
3481 cactcagacc cactcagcca aatctcatgg aagaccaagg agggcagcac tgtttttgtt
3541 ttttgttttt tgtttttttt ttttgacact gtccaaaggt tttccatcct gtccctggaat
3601 cagagttgga agctgaggag cttcagcctc ttttatggtt taatggccac ctgttctctc
3661 ctgtgaaagg ctttgcaaag tcacattaag tttgcatgac ctgttatccc tggggcccta
3721 tttcatagag gctggcccta ttagtgattt ccaaaaacaa tatggaagtg ccttttgatg
3781 tcttacaata agagaagaag ccaatggaaa tgaaagagat tggcaaaggg gaaggatgat
3841 gccatgtaga tcctgtttga catttttatg gctgtatttg taaacttaaa cacaccagtg
3901 tctgttcttg atgcagttgc tatttaggat gagttaagtg cctggggagt cctcaaaaag
3961 gttaaaggga ttcccatcat tggaaatctta tcaccagata ggcaagttta tgaccaaaaca
4021 agagagtact ggcttttatcc tctaacctca tattttctcc cacttggcaa gtcccttgtg
4081 gcatttatcc atcagtcagg gtgtccgatt ggtcctagaa cttccaaagg ctgcttgtca
4141 tagaagccat tgcattctata aagcaacggc tcctgttaaa tggatatccc tttctgaggc
4201 tcctactaaa agtcatttgt tacctaaact tatgtgctta acaggcaatg cttctcagac
4261 cacaagcag aaagaagaag aaaagctcct gactaaatca gggctgggct tagacagagt
4321 tgatctgtag aatatcttta aaggagagat gtcaactttc tgcaactatc ccagcctctg
4381 ctccctccctg tctaccctct cccctccctc tctccctcca cttcacccca caatcttgaa
4441 aaacttcctt tctcttctgt gaacatcatt ggccagatcc attttcagtg gtctggattt
4501 ctttttattt tcttttcaac ttgaaaagaaa ctggacatta ggccactatg tgtgttaact
4561 gccactagtg ttcaagtgcc tcttgttttc ccagagattt cctgggtctg ccagaggccc
4621 agacaggctc actcaagctc tttaaactgaa aagcaacaag ccactccagg acaaggttca
4681 aaatggttac aacagcctct acctgtcgcc ccaggagaa aggggtagtg atacaagtct
4741 catagccaga gatggttttc cactccttct agatattccc aaaaagaggc tgagacagga
4801 ggttattttc aattttattt tggaaattaaa tacttttttc cctttattac tgttgtagt
4861 cctcacttgg atatacctct gttttcacga tagaaataag ggagggtotag agcttctatt
4921 ccttggccat tgtcaacgga gagctggcca agtcttcaca aacccttgca acattgcctg
4981 aagtttatgg aataagatgt attctcactc ccttgatctc aagggcgtaa ctctggaagc
5041 acagcttgac tacacgtcat ttttaaccaat gattttcagg tgacctgggc taagtcattt
5101 aaactgggtc tttataaaaag taaaaggcca acatttaatt attttgcaaa gcaacctaaag
5161 agctaaaagat gtaatttttc ttgcaattgt aaatcttttg tgtctcctga agacttcctc
5221 taaaatttagc tctgagtga aaatcaaaaag agacaaaaga catcttcgaa tccatatttc
5281 aagcctggta gaattggctt ttctagcaga acctttccaa aagttttata ttgagattca
5341 taacaacacc aagaattgat tttgtagcca acattcattc aatactgtta tatcagagga
5401 gtaggagaga ggaaacattt gacttatctg gaaaagcaaa atgtacttaa gaataagaat
5461 aacatgggtcc attcaccttt atgttataga tatgtctttg tgtaaatcat ttgttttgag
5521 ttttcaaaga atagcccatt gttcattctt gtgctgtaca atgaccactg ttattgttac
5581 tttgactttt cagagcacac ccttccctct gtttttgtat atttattgat ggatcaataa
5641 taatgaggaa agcatgatat gtatattgct gagttgaaag cacttatttg aaaatattaa
5701 aaggctaaca ttaaaagact aaaggaaaca gaaaaaaaaa aaaaaaaa

Figure 1-19

CTSC

LOCUS NM_001814 1924 bp mRNA linear PRI 06-APR-2008
 DEFINITION Homo sapiens cathepsin C (CTSC), transcript variant 1, mRNA.
 ACCESSION NM_001814
 VERSION NM_001814.3 GI:167000478

```

1  cgtagctatt tcaaggcgcg cgcctcgtgg tggactcacc gctagcccg c agcgctcggc
61  ttccctggtaa ttcttcacct cttttctcag ctccctgcag catgggtgct gggccctcct
121  tgctgctcgc cgccctcctg ctgcttctct ccggcgacgg cgccgtgcgc tgcgacacac
181  ctgccaactg cacctatctt gacctgctgg gcacctgggt cttccagggt ggctccagcg
241  gttccacgag cgatgtcaac tgctcggtta tgggaccaca agaaaaaaaa gtagtgggtg
301  accttcagaa gctggataca gcatatgatg accttggcaa ttctggccat ttcaccatca
361  tttacaacca aggctttgag attgtgttga atgactacaa gtggtttgcc ttttttaagt
421  ataaagaaga gggcagcaag gtgaccactt actgcaacga gacaatgact ggggtgggtgc
481  atgatgtgtt gggccggaac tgggcttggt tcaccggaaa gaagggtgga actgcctctg
541  agaattgtgt tgtcaacata gcacacctta agaatttctc ggaaaagtat tctaattaggc
601  tctacaagta tgatcacaac tttgtgaaag ctatcaatgc cattcagaag tcttggactg
661  caactacata catggaatat gagactctta ccctgggaga tatgattagg agaagtgggt
721  gccacagtcg aaaaatccca aggccaaac ctgcaccact gactgctgaa atacagcaaa
781  agattttgca tttgccaaac tcttgggact ggagaaatgt tcatgggtatc aattttgtca
841  gtcctgttgc aaaccaagca tcctgtggca gctgctactc atttgcttct atgggtatgc
901  tagaagcgag aatccgtata ctaaccaaca attctcagac cccaatccta agccctcagg
961  aggttgtgtc ttgtagccag tatgctcaag gctgtgaagg cggttcccca taccttattg
1021  caggaaaagta cgcccaagat tttgggctgg tggagaagc ttgcttcccc tacacaggca
1081  ctgattctcc atgcaaaatg aaggaagact gctttcgtta ttactcctct gagtaccact
1141  atgtaggagg tttctatgga ggctgcaatg aagccctgat gaagcttgag ttggtccatc
1201  atggggccat ggcagttgct tttgaagtat atgatgactt cctccactac aaaaagggga
1261  tctaccacca cactggtcta agagaccctt tcaaccctt tgagctgact aatcatgctg
1321  ttctgcttgt gggctatggc actgactcag cctctgggat ggattactgg attgttaaaa
1381  acagctgggg caccggctgg ggtgagaatg gctacttccg gatccgcaga ggaactgatg
1441  agtgtgcaat tgagagcata gcagtggcag ccacaccaat tcctaaattg tagggtatgc
1501  cttccagtat ttcataatga tctgcatcag ttgtaaaggg gaattggtat attcacagac
1561  tgtagacttt cagcagcaat ctcagaagct tacaaataga tttccatgaa gatatttgtc
1621  ttcagaatta aaactgcctt taattttaat atacctttca atcggccact ggccattttt
1681  ttctaagtat tcaattaagt gggaattttc tggaagatgg tcagctatga agtaatagag
1741  tttgcttaat catttgtaat tcaaacatgc tatatttttt aaaatcaatg tgaacacata
1801  gacttatttt taaattgtac caatcacaa gaaaataatg caataattat caaaactttt
1861  aaaatagatg ctcatatttt taaaataaag ttttaaaaat aactgcaaaa aaaaaaaaaa
1921  aaaa

```

Figure 1-20

UAP1

LOCUS NM_003115 2344 bp mRNA linear PRI 22-OCT-2008
 DEFINITION Homo sapiens UDP-N-acetylglucosamine pyrophosphorylase 1 (UAP1), mRNA.
 ACCESSION NM_003115
 VERSION NM_003115.4 GI:156627574

```

1  cgggcgcctc cgcgtccgcg tcgtcgtctg tgctcccggc gctgacgtgt ctgggcggctc
61  ggcttccact ccttcaggcg tcggcagcca ctagtctgtg cgagaggggc ggggtggccg
121  gggctggcgc tccacttggc ccccgctccc ggcccgcgcc gccgcgcggg cccccggat
181  gaggttatat attcggagcg agcgcgggac gccgatgagt ggccgcgcgg aaggagctgg
241  agacggtcgt agctgcggtc gcgccgagaa aggtttacag gtacatacat tacacccta
301  tttctacaaa gcttggctat tagagcatta tgaacattaa tgacctcaaa ctcacgttgt
361  ccaaagctgg gcaagagcac ctactacgtt tctggaatga gcttgaagaa gcccaacagg
421  tagaacttta tgcagagctc caggccatga actttgagga gctgaacttc tttttccaaa
481  aggccattga aggttttaac cagtcttctc accaaaagaa tgtggatgca cgaatggaac
541  ctgtgcctcg agaggtatta ggcagtgcta caagggatca agatcagctc caggcctggg
601  aaagtgaagg acttttccag atttctcaga ataaagtagc agttcttctt ctagctggtg
661  ggcaggggac aagactcggc gttgcatatc ctaaggggat gtatgatgtt ggtttgccat
721  cccgtaagac actttttcag attcaagcag agcgtatcct gaagctacag caggttgctg
781  aaaaatatta tggcaacaaa tgcattattc catggtatat aatgaccagt ggcagaacaa
841  tggaatctac aaaggagttc ttcaccaagc acaagtactt tggtttaaaa aaagagaatg
901  taatcttttt tcagcaagga atgtcccccg ccatgagttt tgatgggaaa attattttgg
961  aagagaagaa caaagtttct atggctccag atgggaatgg ttggtctttat cgggcacttg
1021  cagcccagaa tattgtggag gatatggagc aaagaggcat ttggagcatt catgtctatt
1081  gtgttgacaa catattagta aaagtggcag acccacggtt cattggattt tgcattcaga
1141  aaggagcaga ctgtggagca aaggtggtag agaaaaacgaa ccctacagaa ccagttggag
1201  tggtttgccg agtggatgga gtttaccagg tggtagaata tagtgagatt tccctggcaa
1261  cagctcaaaa acgaagctca gacggaacgac tgctgttcaa tgcggggaac attgccaac
1321  atttcttcac tgtaccattt ctgagagatg ttgtcaatgt ttatgaacct cagttgcagc
1381  accatgtggc tcaaaagaag attccttatg tggataccca aggacagtta attaagccag
1441  acaaacccaa tgggaataaag atggaaaaat ttgtctttga catcttccag tttgcaaaga
1501  agtttgtggt atatgaagta ttgcgagaag atgagtttcc cccactaaag aatgctgata
1561  gtcagaatgg gaaagacaac cctactactg caaggcatgc tttgatgtcc cttcatcatt
1621  gctgggtcct caatgcaggg ggccatttca tagatgaaaa tggctctcgc cttccagcaa
1681  ttcccgcgtt gaaggatgcc aatgatgtac caatccaatg tgaaatctct cctcttatct
1741  cctatgctgg agaaggatta gaaagttagt tggcagataa agaattccat gcacctctaa
1801  tcatcgatga gaatggagtt catgagctgg tgaaaaatgg tatttgaaac agataccaag
1861  ttttgtttgc cacgatagga atagctttta tttttgatag accaactgtg aacctacaag
1921  acgtcttgga caactgaagt ttaaatatcc acagggtttt attttgcttg ttgaactctt
1981  agagctattg caaacttccc aagatccaga tgactgaatt tcagatagca tttttatgat
2041  tcccaactca ttgaaggtct tatttatata attttttcca agccaaggag accattggcc
2101  atccaggaaa tttcgtacag ctgaaatata ggcaggatgt tcaacatcag tttacttgca
2161  gctggaagca tttgtttttg aagttgtaca tagtaataat atgtcattgt acatgttgaa
2221  aggtttctat ggtactaaaa gtttgtttta ttttatcaaa cattaagctt ttttaagaaa
2281  ataattgggc agtgaaataa atgtatcttc ttgtctctgg agtgtcaaaa aaaaaaaaaa
2341  aaaa

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Figure 1-21

PUS7

LOCUS NM_019042 3484 bp mRNA linear PRI 11-FEB-2008
DEFINITION Homo sapiens pseudouridylylate synthase 7 homolog (S. cerevisiae) (PUS7), mRNA.
ACCESSION NM_019042 XM_496914 XM_499357
VERSION NM_019042.3 GI:50727001

```
1  gtgcgagccc ggccgccggt gagtcggctg gagcgcacat ggtcctccgc gcggaaagcg
61  ctgcttttgc ctggccgccc tagccgctgg ctcacccaag tggccttcgc cgctctcttg
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Figure 1-22

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Figure 1-23

CD22

LOCUS NM_001771 3293 bp mRNA linear PRI 16-MAR-2008
 DEFINITION Homo sapiens CD22 molecule (CD22), mRNA.
 ACCESSION NM_001771
 VERSION NM_001771.2 GI:157168354

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Figure 1-24

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Figure 1-25

RGS13

LOCUS NM_144766 1458 bp mRNA linear PRI 31-JAN-2010
DEFINITION Homo sapiens regulator of G-protein signaling 13 (RGS13),
transcript variant 2, mRNA.
ACCESSION NM_144766
VERSION NM_144766.1 GI:21464138
KEYWORDS .
SOURCE Homo sapiens (human)

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Figure 1-26

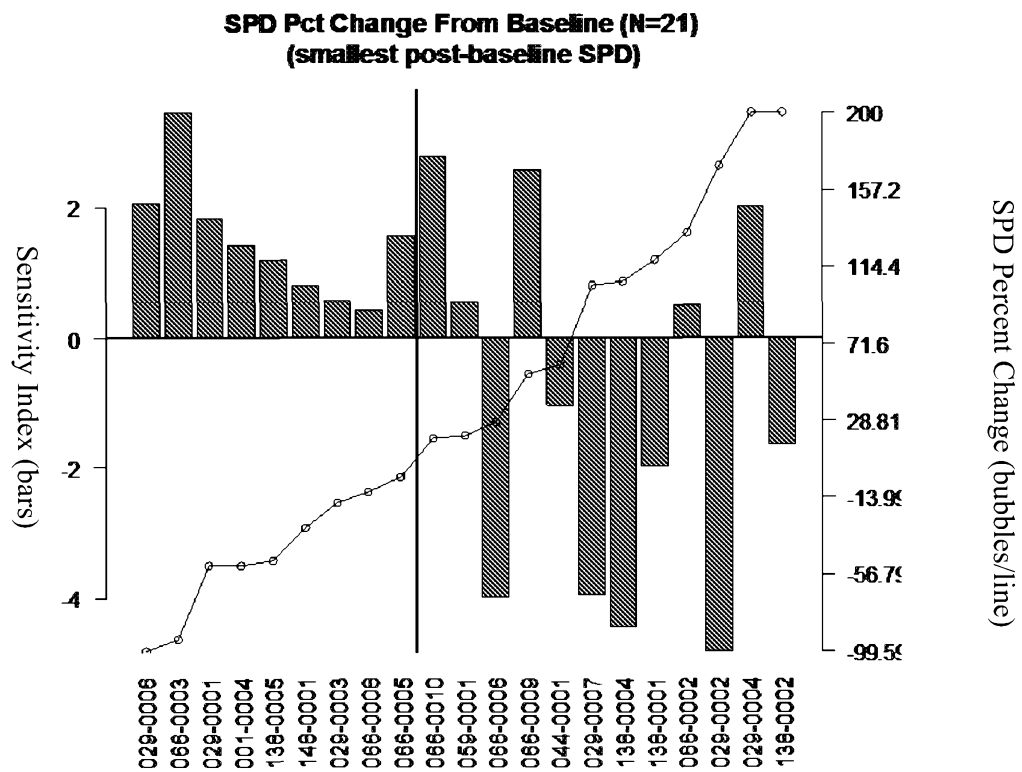


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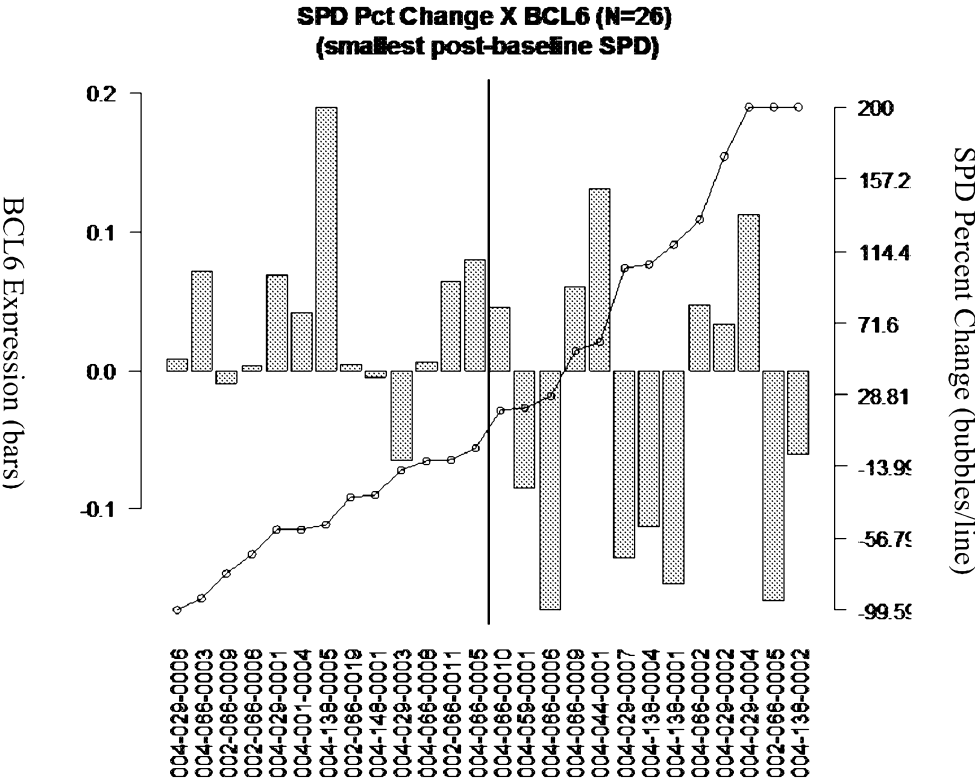


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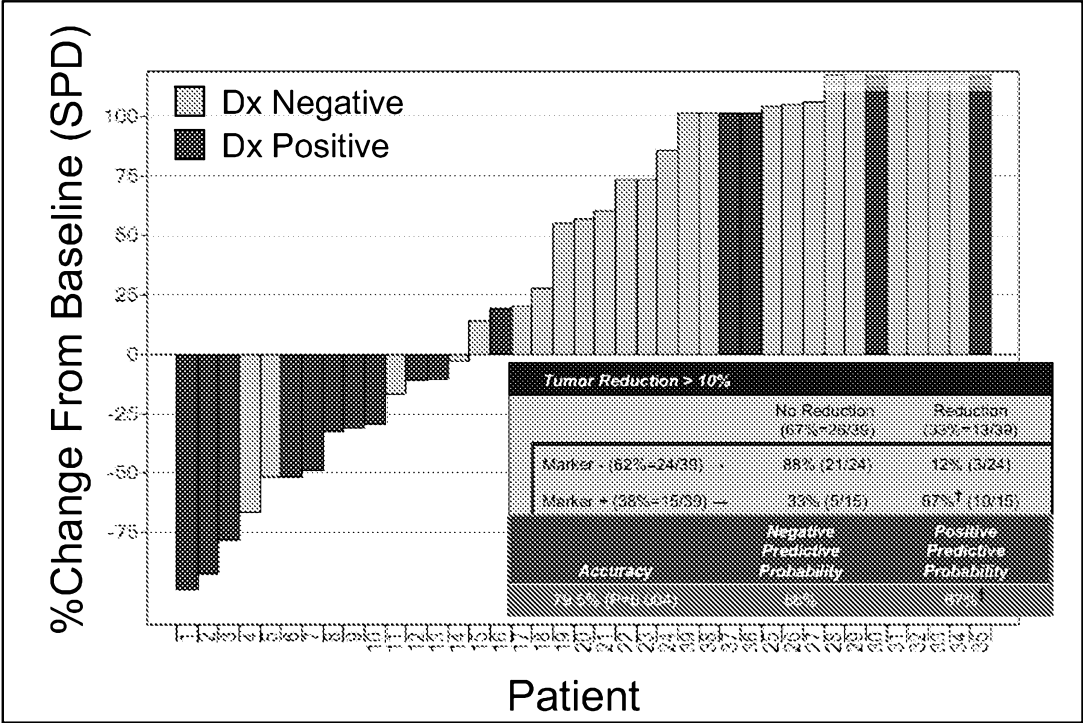
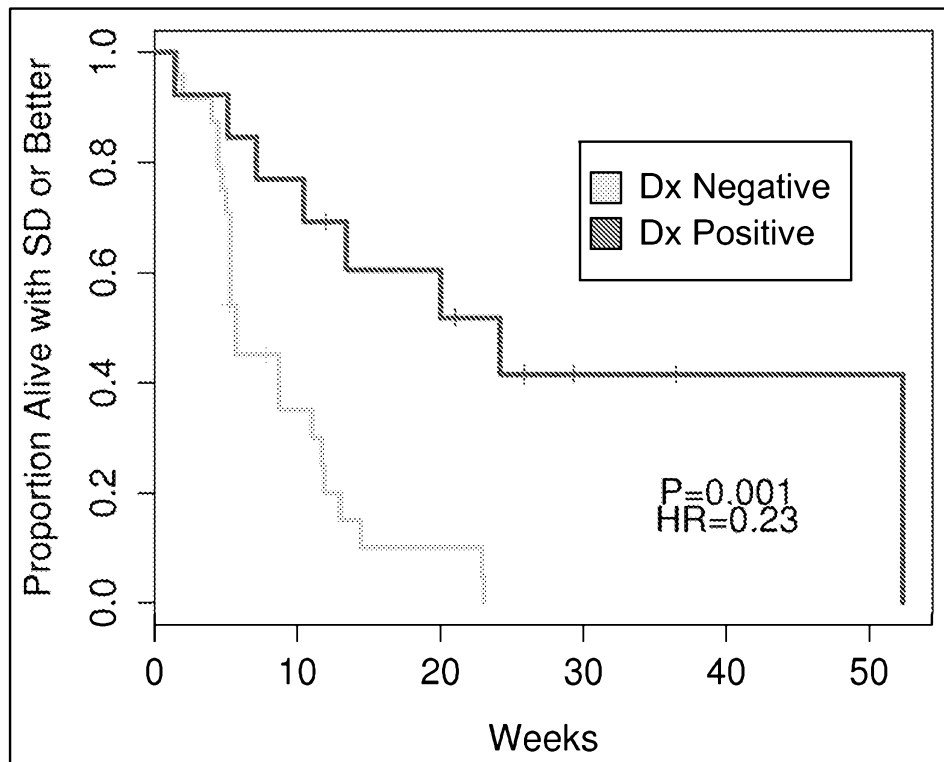


Figure 4

**Figure 5**

08 Apr 2013
2010236168

2885200_1

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<110> GENENTECH, INC.
DORNAN, David
BURLINGTON, Bruce

<120> METHODS FOR ASSESSING RESPONSIVENESS OF
B-CELL LYMPHOMA TO TREATMENT WITH ANTI-CD40 ANTIBODIES

<130> 146392006940

<140> PCT/US2010/031528

<141> 2010-04-17

<150> US 61/170,615

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<160> 274

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2885200_1

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<213> Homo sapiens

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