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

(57) **Abrégé/Abstract:**

The invention provides methods and kits useful for predicting or assessing responsiveness of B-cell lymphoma to treatment with anti-CD40 antibodies.

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

RELATED APPLICATIONS

[0001] This application claims benefit of provisional application serial number 60/986,277, filed on November 7, 2007.

TECHNICAL FIELD

[0002] The present invention relates generally to the fields of predicting, assessing, aiding assessment of responsiveness of B-cell lymphoma to treatment with anti-CD40 antibodies.

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<sup>+</sup> 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

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(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.

[0006] Seattle Genetics initiated Phase I clinical trials in 2004 with the humanized anti-CD40 antibody in a single agent multi-dose trial in patients with relapsed and refractory multiple myeloma (MM). Subsequently, Phase I trials were initiated in patients with relapsed non-Hodgkin's lymphoma (NHL) and chronic lymphocytic lymphoma (CLL). The results from these Phase I trials showed evidence for anti-tumor activity in myeloma patients with stable disease and decreased M-protein, NHL patients with partial and complete responses, and CLL patients with stable disease. A phase II trial of the anti-CD40 antibody in relapsed diffuse large B cell lymphoma (DLBCL) was initiated in December 2006.

[0007] 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 anti-CD40 antibody therapy.

[0008]

#### SUMMARY OF THE INVENTION

[0009] 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.

[0010] In one aspect, the invention provides 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 in any of Tables 2-4, 6, 7 and 13 in a B-cell lymphoma sample from the subject to a reference level.

[0011] In another aspect, the invention provides 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 in any of Tables 2-4, 6, 7 and 13 in a B-cell lymphoma sample from the subject to a reference level.

**[0012]** In another aspect, the invention provides 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 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, and PUS7; (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, or fourteen 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.

**[0013]** In another aspect, the invention provides methods preparing a personalized genomics profile for a subject having B-cell lymphoma comprising the steps of: (a) determining 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 the 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.

**[0014]** In another aspect, the invention provides 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 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, and PUS7 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 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 13 are measured;

wherein (i)  $\beta_j$  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)  $\mu_j$  and  $\sigma_j$  are means and standard deviations for each marker gene measured; wherein  $\beta_j$ ,  $\mu_j$  and  $\sigma_j$  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 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. In some embodiments, the expression level 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, or fourteen 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.

**[0015]** In another aspect, the invention provides methods for treating a subject having a B-cell lymphoma, comprising administering an effective amount of the 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. In another aspect, the invention provides methods for treating a subject having a 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 in any of Tables 2-4, 6, 7 and 13 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.

**[0016]** In some embodiments, the reference level is a measured expression level of one or more reference genes in Table 8 or Table 9 in the B-cell lymphoma sample from the subject.

**[0017]** 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.

**[0018]** In some embodiments, the measured expression level of the marker gene and/or the reference level are normalized.

**[0019]** In some embodiments, measured expression levels of at least two, at least five, at least ten, at least fifteen, or at least twenty genes in any of Tables 2-4, 6, 7 and 13 in the B-cell lymphoma sample from the subject are compared to one or more reference levels.

**[0020]** 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)).

**[0021]** In some embodiments, the marker genes measured comprise one or more CD40 ligand downregulated genes (e.g., VNN2, MEF2C, LTB, KCNN3, NCF1, BCL6, IGJ, ELTI1902, PNOC, CSF2RB, and POU2AF1). In some embodiments, the marker genes measured comprise one or more genes in the B-cell receptor signaling pathway (e.g., CD22, RGS13, and MEF2B).

**[0022]** In some embodiments, expression levels 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, or fourteen genes selected from the group consisting of VNN2, MEF2C, LTB, KCNN3, NCF1, BCL6, IGJ, ELTI1902, PNOC, CSF2RB, POU2AF1, CD22, RGS13, and MEF2B in the B-cell lymphoma sample from the subject are compared to one or more reference levels.

**[0023]** In some embodiments, expression levels of one or more gene pairs selected from the group consisting of VNN2 and EPDR1, RGS13 and EPDR1, CD22 and EPDR1, LRRC8A

and PRPSAP2, CD40 and IGF1R, IFITM1 and BTG2, SMN1 and LMO2, PRKCA and YIPF3 in a the B-cell lymphoma sample are compared. In some embodiments, expression levels are compared between one or more gene pairs VNN2 and EPDR1, RGS13 and EPDR1, CD22 and EPDR1, LRRC8A and PRPSAP2, CD40 and IGF1R, IFITM1 and BTG2, SMN1 and LMO2, PRKCA and YIPF3 in the B-cell lymphoma sample, and sensitivity index calculated as the sum of signed t-scores for log2-scale expression of the gene pairs is used to assess responsiveness of the B-cell lymphoma to an anti-CD40 antibody treatment.

**[0024]** In some embodiments, the 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. In some embodiments, the B-cell lymphoma is selected from the group consisting of indolent lymphoma, aggressive lymphoma, and highly aggressive lymphoma.

**[0025]** In a further aspect, the invention provides kits comprising reagents for measuring expression levels of at least one marker gene in any of Tables 2-4, 6, 7 and 13. In some embodiments, the kits comprise at least a pair of primers for amplifying by PCR at least one marker gene in any of Tables 2-4, 6, 7 and 13. For example, forward and reverse primers shown in Table 10 may be used. The kits may further comprise a pair of primers for amplifying a reference gene in Table 8. 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 in any of Tables 2-4, 6, 7 and 13 by qRT-PCR. The kits may further comprise a pair of primers and a probe for detecting expression level of a reference gene in Table 8 by qRT-PCR. For example, primer and probe sets shown in Table 10 may be used for detection expression level of genes 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.

**[0026]** 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.

[0026A] The present invention as claimed relates to:

- a method for predicting responsiveness of a subject having a B-cell lymphoma to an agonist anti-CD40 antibody treatment, comprising the steps of: (a) measuring expression level of one or more pairs of marker genes in a sample comprising B lymphoma cells obtained from said subject, wherein said one or more pairs of marker genes are selected from the group consisting of IFITM1 and BTG2, CD40 and IGF1R, RGS13 and CD44, VNN2 and CTSC, LMO2 and EPDR1, CD79B and UAP1, and CD22 and PUS7; 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 pairs of marker genes from step (a);

- a method for predicting responsiveness of a subject having a B-cell lymphoma to an agonist anti-CD40 antibody treatment, comprising the steps of: (a) measuring the expression level of one or more pairs of marker genes in a sample comprising B lymphoma cells from the subject, wherein said one or more pairs of marker genes are selected from the group consisting of IFITM1 and BTG2, CD40 and IGF1R, RGS13 and CD44, VNN2 and CTSC, LMO2 and EPDR1, CD79B and UAP1, and CD22 and PUS7; and (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 (i)  $\beta_j$  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)  $\mu_j$  and  $\sigma_j$  are means and standard deviations for each marker gene measured; wherein  $\beta_j$ ,  $\mu_j$  and  $\sigma_j$  are determined from patient samples comprising B lymphoma cells from a clinical trial; and wherein a value equal to 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 the anti-CD40 antibody treatment; and

- a kit comprising reagents for measuring expression level of one or more pairs of marker genes in a sample comprising B lymphoma cells from a subject, wherein said one or more pairs of marker genes are selected from the group consisting of IFITM1 and BTG2, CD40 and IGF1R, RGS13 and CD44, VNN2 and CTSC, LMO2 and EPDR1, CD79B and UAP1, and CD22 and PUS7, wherein the kit further comprises instructions for assessing if a human subject having a B-cell lymphoma is likely to respond to an agonist anti-CD40 antibody treatment based on the expression level of said one or more pairs of markers genes.

### BRIEF DESCRIPTION OF THE FIGURES

**[0027]** Figure 1. Enrichment plot of genes within BASSO\_GERMINAL\_CENTER\_CD40\_DN gene set. The upper plot represents the enrichment score distribution across the ranked genes from the moderated t-test (Table 2). The lower plot displays the distribution of the enrichment with respect to a ranked list metric known as signal2noise. Overall, these plots clearly show that the gene set is strongly enriched within anti-CD40 Ab.1 sensitive cells.

**[0028]** Figure 2. VNN2, a CD40L-downregulated gene, is overexpressed in sensitive NHL cells to anti-CD40 Ab.1 and discriminates between the two classes of sensitive and resistant. The bar graph represents the mRNA expression level and the line graph represents the IC25 values.

**[0029]** Figure 3A-3C. RGS13, CD22, and MEF2B germinal center B markers, are overexpressed in sensitive and intermediate NHL cells to anti-CD40 Ab.1 and can discriminate with reasonable accuracy between the two classes of sensitive and resistant. The bar graph represents the mRNA expression level and the line graph represents the IC25 values.

**[0030]** Figure 4. Anti-CD40Ab.1 Sensitivity Index Scoring Across NHL Cell Lines. Stepwise Linear Modeling and gene-pair scoring was applied to each cell line based on mRNA expression data. The primary y-axis displays the anti-CD40 Ab.1 Sensitivity Index and the secondary y-axis displays the anti-CD40 Ab.1 IC25 values plotted against the NHL cell lines on the x-axis. A high anti-CD40 Ab.1 Sensitivity Index ( $> -4$ ) represents an increased probability of a cell line being sensitive.

**[0031]** Figure 5. Correlation of CD40 signature genes with anti-CD40.Ab.1 sensitivity.

**[0032]** Figure 6-1 to 6-35. Gene bank sequences for genes listed in Table 7 and Table 10. Nucleic acid sequences encoding mRNA of VNN2 (Figure 6-1: SEQ ID NO:258), RGS13 (Figure 6-2: SEQ ID NO:259), CD22 (Figure 6-3 and 6-4: SEQ ID NO:260), LRRC8A (Figure 6-5: SEQ ID NO:261), CD40 (Figure 6-6: SEQ ID NO:262), IFITM1 (Figure 6-7: SEQ ID NO:263), PRKCA (Figure 6-8 to 6-10: SEQ ID NO:264), BCL6 (Figure 6-11 and 6-12: SEQ ID NO:265), EPDR1 (Figure 6-13: SEQ ID NO:266), PRPSAP2 (Figure 6-14: SEQ ID NO:267), IGF1R (Figure 6-15 to 6-18: SEQ ID NO:268), BTG2 (Figure 6-19 and 6-20: SEQ ID NO:269), LMO2 (Figure 6-21: SEQ ID NO:270), YIPF3 (Figure 6-22: SEQ ID NO:271), SMN1 (Figure 6-23: SEQ ID NO:272), CD79B (Figure 6-24: SEQ ID NO:273), CD44 (Figure 6-25 and 6-26: SEQ ID NO:274), CTSC (Figure 6-27: SEQ ID NO:275),

UAP1 (Figure 6-28: SEQ ID NO:276), PUS7 (Figure 6-29 and 6-30: SEQ ID NO:277), RGS13 (Figure 6-31: SEQ ID NO:278), CD22 (Figure 6-32 and 6-33: SEQ ID NO:279), SMN1 (Figure 6-34: SEQ ID NO:280), and YIPF3 (Figure 6-35: SEQ ID NO:281).

**[0033]** Figure 7. 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 14. Larger multivariate sensitivity index values are associated with SPD decreases post-baseline (Sperman's  $Rho = -0.58$ ;  $P=0.006$ ).

**[0034]** Figure 8. Association of BCL6 expression and percent change in SPD measurements for 26 patients with DLBCL. 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.

### DETAILED DESCRIPTION

**[0035]** The present invention is based on the discovery that certain genes (*e.g.*, genes shown in Tables 2-4, 6, 7 and 13) 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 Example 2 indicate that the expression level of the fourteen genes shown in Table 13 is highly associated with responsiveness to 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 a 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**

**[0036]** 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).

**[0037]** Primers, oligonucleotides and polynucleotides employed in the present invention can be generated using standard techniques known in the art.

**[0038]** 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**

**[0039]** 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.

**[0040]** 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.

**[0041]** 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.

**[0042]** 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.

**[0043]** 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.

**[0044]** 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.

**[0045]** 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.

**[0046]** 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).

**[0047]** 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.

**[0048]** 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.

**[0049]** “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.

**[0050]** 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.

**[0051]** "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, poly-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,  $\alpha$ -anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S("thioate"), P(S)S("dithioate"), "(O)NR<sub>2</sub>("amidate"), P(O)R, P(O)OR', CO or CH<sub>2</sub>("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.

**[0052]** "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.

**[0053]** 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.

**[0054]** 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.

**[0055]** 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.

**[0056]** "Detection" includes any means of detecting, including direct and indirect detection.

**[0057]** 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.

**[0058]** 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.

**[0059]** "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.

**[0060]** 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.

**[0061]** "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')<sub>2</sub>, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

**[0062]** "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.

**[0063]** 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).

**[0064]** 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.

**[0065]** "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).

**[0066]** 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.

**[0067]** 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).

**[0068]** 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.

**[0069]** 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.

**[0070]** “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).

**[0071]** “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.

**[0072]** 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.

**[0073]** 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.

**[0074]** 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.

**[0075]** 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.

[0076] 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.

[0077] As used herein, "a", "an", and "the" can mean singular or plural (*i.e.*, can mean one or more) unless indicated otherwise.

### **C. Methods of the Invention**

[0078] The invention provides methods for assessing or aiding assessment of responsiveness of a subject having a 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 a B-cell lymphoma. The invention provides methods for selecting a subject having a B-cell lymphoma suitable for treatment with an anti-CD40 antibody and following up with an anti-CD40 antibody treatment. In some embodiments, the methods comprise measuring expression level of one or more marker genes in any of Tables 2-4, 6, 7, and 13 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 a measured expression level of at least one marker gene in any of Tables 2-4, 6, 7, and 13 in a B-cell lymphoma sample from the subject to a reference level for the respective marker gene.

[0079] The methods of the present invention are useful for clinicians to identify patients with B-cell lymphoma for treatment with an anti-CD40 antibody, aiding in patient selection during the course of development of anti-CD40 antibody therapy, prediction of likelihood of success when treating an individual patient with a particular treatment regimen, in assessing and monitoring disease progression, in monitoring treatment efficacy, and in determining prognosis for individual patients. Any of these embodiments are included in this invention.

[0080] In some embodiments, the 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.

[0081] In some embodiments, the B-cell lymphoma is indolent. In some embodiments, the B-cell lymphoma is aggressive. In some embodiments, the B-cell lymphoma is highly aggressive. In some embodiments, the indolent B-cell lymphoma is follicular lymphoma, marginal zone lymphoma, or small lymphocytic lymphoma. In some embodiments, the indolent B-cell lymphoma is follicular lymphoma.

#### Marker genes

[0082] The expression level of one or more of the marker genes in a B-cell lymphoma sample relative a reference level 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.

[0083] Genes that are differentially expressed (statistically significantly increased or decreased) in anti-CD40 antibody sensitive NHL cell lines as compared to resistant NHL cell lines are shown in Tables 2-4, 6 and 7. “Anti-CD40 antibody sensitive cells” are cells having an IC25 value less than 0.4 µg/ml in reduction of cell viability by an anti-CD40 antibody tested as described in Example 1. “Anti-CD40 resistant cells” are cells having an IC25 value greater than 1 µg/ml in reduction in cell viability as tested in Example 1. Some of the genes in Tables 2-4, 6 and 7 are in the CD40 ligand downregulated pathway (for example, VNN2, MEF2C, LTB, KCNN3, NCF1, BCL6, IGJ, ELTI1902, PNOC, CSF2RB, and POU2AF1); and some of the genes in the tables are in the B-cell receptor signaling pathway (for example, CD22, RGS13, and MEF2B). Further, association of the expression level of IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7 (Table 13) has been confirmed by clinical trials described in Example 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, at least fifteen, at least twenty, at least twenty five, or at least thirty genes are used in the methods of the invention.

[0084] In some embodiments, expression levels of one or more of genes selected from the group consisting of VNN2, MEF2C, LTB, KCNN3, NCF1, BCL6, IGJ, ELTI1902, PNOC, CSF2RB, POU2AF1, CD22, RGS13, and MEF2B are measured and/or used. In some embodiments, expression levels of one or more of genes selected from the group consisting

of IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7 are measured and/or used. 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, or fourteen of these genes are measured and/or used. In some embodiments, expression levels of CD22, CD40, and BCL6 are measured and/or used. In some embodiments, expression levels of CD40, RGS13, CD22, BTG2, IGF1R, and CD44 are measured and/or used. In some embodiments, expression levels of IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7 are measured and/or used. In some embodiments, expression levels 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 of genes in Table 7 or Table 13 are measured and/or used.

**[0085]** Genes (including sequences) identified in Tables 2-4, 6, 7 and 13 are known in the art. For example, the examples of Gene Bank 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).

**[0086]** The nucleic acid sequence of some of the genes referenced in Tables 2-4, 6, 7 and 13 are shown in Figure 6 (6-1 to 6-35).

#### Reference levels

**[0087]** 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 shown in Table 8 are used as reference levels. In some embodiments, expression levels of one or more housekeeping genes shown in Table 9 are used as reference levels.

**[0088]** 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.

**[0089]** The reference genes in Table 8 and Table 9 were selected as specific normalizing counterparts to the marker genes in Table 4. 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 in Table 4.

**[0090]** 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.

**[0091]** 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.

Table 8.

| Probe                            | VarW.<br>VarB | mean  | var  | vscr  | vscr<br>rank | P.Min    | SCR.<br>anti-<br>CD40.<br>Ab.1 | IC25.<br>anti-<br>CD40.<br>Ab.1 | GCB.<br>anti-<br>CD40.<br>Ab.1 | SCR<br>EXT.<br>anti-<br>CD40.<br>Ab.1 |
|----------------------------------|---------------|-------|------|-------|--------------|----------|--------------------------------|---------------------------------|--------------------------------|---------------------------------------|
| 202521_at                        | 0.02          | 10.61 | 0.19 | -3.81 | 5079         | 0.020543 | 0.896744                       | 0.758931                        | 0.927787                       | 0.285815                              |
| 201949_x_at                      | 0.04          | 11.78 | 0.33 | 7.92  | 300          | 0.363476 | 0.5627                         | 0.9554                          | 0.3785                         | 0.3635                                |
| 201588_at                        | 0.01          | 13.00 | 0.29 | -2.39 | 3182         | 2.49E-09 | 0.2422                         | 0.5231                          | 0.2540                         | 0.1104                                |
| 201070_x_at                      | 0.20          | 9.46  | 0.23 | -3.78 | 5023         | 0.089689 | 0.1715                         | 0.1517                          | 0.2230                         | 0.5294                                |
| 209180_at                        | 0.23          | 10.80 | 0.40 | -2.89 | 3693         | 0.001233 | 0.9074                         | 0.9214                          | 0.7339                         | 0.1495                                |
| AFFX-<br>HSAC07/<br>X00351_5_at  | 0.03          | 14.02 | 0.53 | 0.48  | 2039         | 0.144577 | 0.6074                         | 0.9584                          | 0.2415                         | 0.4461                                |
| 201891_s_at                      | 0.13          | 14.67 | 0.22 | 1.98  | 1919         | 0.010118 | 0.2646                         | 0.1011                          | 0.4501                         | 0.0392                                |
| FFX-<br>HUMGAPDH/<br>M33197_5_at | 0.59          | 14.78 | 0.04 | 2.95  | 1850         | 0.000944 | 0.7089                         | 0.7244                          | 0.9014                         | 0.3096                                |
| 202605_at                        | 0.05          | 10.52 | 0.65 | -3.44 | 4415         | 6.73E-05 | 0.0096                         | 0.0104                          | 0.0053                         | 0.0885                                |
| 202854_at                        | 0.03          | 12.92 | 0.30 | -1.90 | 2773         | 2.64E-05 | 0.1297                         | 0.2069                          | 0.0532                         | 0.5541                                |
| 200737_at                        | 0.02          | 12.20 | 0.46 | -2.75 | 3533         | 0.000307 | 0.0777                         | 0.3535                          | 0.0719                         | 0.6473                                |
| 201293_x_at                      | 0.60          | 14.99 | 0.02 | 3.98  | 1731         | 0.065694 | 0.1406                         | 0.3579                          | 0.1735                         | 0.6190                                |
| 201033_x_at                      | 0.62          | 15.20 | 0.01 | 4.16  | 1709         | 0.066741 | 0.0667                         | 0.1150                          | 0.1081                         | 0.7451                                |
| 203135_at                        | 0.06          | 8.29  | 0.19 | -     | 21417        | 0.001289 | 0.6978                         | 0.7904                          | 0.8630                         | 0.2849                                |
|                                  |               |       |      | 16.66 |              |          |                                |                                 |                                |                                       |
| 207332_s_at                      | 0.06          | 12.50 | 1.16 | -0.82 | 2311         | 5.66E-06 | 0.1391                         | 0.0963                          | 0.1051                         | 0.1710                                |
| 226131_s_at                      | 0.68          | 15.60 | 0.01 | 15.24 | 1            | 0.4182   | 0.6946                         | 0.6783                          | 0.9425                         | 0.4182                                |
| 1553567_s_at                     | 0.53          | 15.77 | 0.04 | 15.10 | 2            | 0.2744   | 0.3205                         | 0.5881                          | 0.2744                         | 0.8039                                |
| 213477_x_at                      | 0.80          | 15.71 | 0.02 | 14.94 | 3            | 0.2716   | 0.3490                         | 0.5611                          | 0.2716                         | 0.9425                                |
| 229563_s_at                      | 0.65          | 15.08 | 0.02 | 14.64 | 4            | 0.2266   | 0.3258                         | 0.2266                          | 0.6668                         | 0.7720                                |
| 203107_x_at                      | 0.75          | 15.37 | 0.01 | 14.55 | 5            | 0.2635   | 0.4033                         | 0.5834                          | 0.2635                         | 0.6664                                |

| Probe        | symb     | VarW.<br>VarB | mean  | var  | vscr  | vscr.<br>rank |  |  | SCR.<br>anti-<br>CD40.<br>Ab.1 | IC25.<br>anti-<br>CD40.<br>Ab.1 | GCB.<br>anti-<br>CD40.<br>Ab.1 | SCR<br>EXT.<br>anti-<br>CD40.<br>Ab.1 |
|--------------|----------|---------------|-------|------|-------|---------------|--|--|--------------------------------|---------------------------------|--------------------------------|---------------------------------------|
| 213614 x at  | EEF1A1   | 0.51          | 16.11 | 0.02 | 14.47 | 6             |  |  | 0.4168                         | 0.5721                          | 0.2273                         | 0.6765                                |
| 204892 x at  | EEF1A1   | 0.55          | 15.29 | 0.02 | 14.46 | 7             |  |  | 0.7883                         | 0.7755                          | 0.5296                         | 0.7598                                |
| 212391 x at  | RPS3A    | 0.78          | 15.00 | 0.01 | 14.34 | 8             |  |  | 0.3159                         | 0.6319                          | 0.2519                         | 0.3350                                |
| 211542 x at  | RPS10    | 0.59          | 15.11 | 0.02 | 14.31 | 9             |  |  | 0.8313                         | 0.9604                          | 0.7117                         | 0.7029                                |
| 213583 x at  | EEF1A1   | 0.66          | 15.26 | 0.04 | 14.29 | 10            |  |  | 0.4132                         | 0.7604                          | 0.2172                         | 0.8064                                |
| 200819 s at  | RPS15    | 0.54          | 15.00 | 0.05 | 13.99 | 11            |  |  | 0.6401                         | 0.7339                          | 0.8220                         | 0.7939                                |
| 200095 x at  | FLJ20294 | 0.60          | 15.29 | 0.02 | 13.98 | 12            |  |  | 0.7334                         | 0.5003                          | 0.4045                         | 0.4757                                |
| 224585 x at  | ACTG1    | 0.49          | 14.73 | 0.06 | 13.96 | 13            |  |  | 0.9612                         | 0.7590                          | 0.4788                         | 0.5097                                |
| 213414 s at  | RPS19    | 0.49          | 15.19 | 0.02 | 13.95 | 14            |  |  | 0.6110                         | 0.5909                          | 0.3134                         | 0.9180                                |
| 1553538 s at | NA       | 0.33          | 15.24 | 0.24 | 13.94 | 15            |  |  | 0.6181                         | 0.5473                          | 0.9966                         | 0.9360                                |
| 200032 s at  | RPL9     | 0.61          | 15.30 | 0.01 | 13.80 | 16            |  |  | 0.7969                         | 0.6658                          | 0.8910                         | 0.9033                                |
| 200063 s at  | NPM1     | 0.68          | 15.34 | 0.02 | 13.78 | 17            |  |  | 0.6557                         | 0.7122                          | 0.2634                         | 0.9201                                |
| 213890 x at  | RPS16    | 0.42          | 15.02 | 0.01 | 13.68 | 18            |  |  | 0.2936                         | 0.2333                          | 0.3297                         | 0.2718                                |
| 212734 x at  | RPL13    | 0.46          | 14.92 | 0.03 | 13.66 | 19            |  |  | 0.8232                         | 0.6720                          | 0.4503                         | 0.7004                                |
| 211983 x at  | ACTG1    | 0.40          | 14.83 | 0.06 | 13.54 | 20            |  |  | 0.9680                         | 0.7211                          | 0.4205                         | 0.7919                                |
| 213801 x at  | RPSA     | 0.61          | 15.01 | 0.05 | 13.53 | 21            |  |  | 0.4603                         | 0.7140                          | 0.2661                         | 0.4003                                |
| 202649 x at  | RPS19    | 0.33          | 15.03 | 0.03 | 13.44 | 22            |  |  | 0.5861                         | 0.5086                          | 0.3172                         | 0.9400                                |
| 221607 x at  | ACTG1    | 0.41          | 14.73 | 0.06 | 13.38 | 23            |  |  | 0.9680                         | 0.6637                          | 0.3927                         | 0.6126                                |
| 212988 x at  | ACTG1    | 0.45          | 14.53 | 0.06 | 13.31 | 24            |  |  | 0.9075                         | 0.6394                          | 0.3553                         | 0.7217                                |
| 208929 x at  | RPL13    | 0.40          | 14.75 | 0.02 | 13.25 | 25            |  |  | 0.3583                         | 0.7912                          | 0.9760                         | 0.6997                                |
| 200689 x at  | EEF1G    | 0.64          | 14.25 | 0.03 | 13.21 | 26            |  |  | 0.9324                         | 0.8163                          | 0.8508                         | 0.3667                                |
| 211345 x at  | EEF1G    | 0.54          | 14.23 | 0.03 | 13.21 | 27            |  |  | 0.9444                         | 0.8022                          | 0.7118                         | 0.3901                                |
| 211970 x at  | ACTG1    | 0.46          | 14.51 | 0.09 | 13.18 | 28            |  |  | 0.7347                         | 0.8427                          | 0.7238                         | 0.5534                                |
| 211995 x at  | ACTG1    | 0.35          | 14.61 | 0.10 | 13.14 | 29            |  |  | 0.5436                         | 0.9959                          | 0.9161                         | 0.3981                                |
| 200089 s at  | RPL4     | 0.29          | 15.28 | 0.04 | 13.09 | 30            |  |  | 0.4500                         | 0.6581                          | 0.5132                         | 0.5295                                |
| 200024 at    | RPS5     | 0.57          | 14.61 | 0.03 | 13.09 | 31            |  |  | 0.7753                         | 0.8060                          | 0.5846                         | 0.9469                                |

| Probe                   | VarW.<br>VarB | mean  | var  | vscr  | vscr<br>rank | P.Min  | SCR.<br>anti-<br>CD40.<br>Ab.1 | IC25.<br>anti-<br>CD40.<br>Ab.1 | GCB.<br>anti-<br>CD40.<br>Ab.1 | SCR<br>EXT.<br>anti-<br>CD40.<br>Ab.1 |
|-------------------------|---------------|-------|------|-------|--------------|--------|--------------------------------|---------------------------------|--------------------------------|---------------------------------------|
| 201550 x at             | 0.33          | 14.50 | 0.10 | 13.04 | 32           | 0.3356 | 0.5966                         | 0.9624                          | 0.8531                         | 0.4378                                |
| AFFX-r2-P1-<br>cre-3 at | 0.28          | 15.23 | 0.12 | 13.00 | 33           | 0.4500 | 0.9518                         | 0.5889                          | 0.7244                         | 0.8836                                |
| 200003 s at             | 0.14          | 15.12 | 0.04 | 12.93 | 34           | 0.5687 | 0.9905                         | 0.6582                          | 0.9539                         | 0.5687                                |
| 212363 x at             | 0.33          | 14.18 | 0.12 | 12.81 | 35           | 0.4219 | 0.6539                         | 0.8152                          | 0.8079                         | 0.4254                                |
| 221775 x at             | 0.28          | 14.55 | 0.05 | 12.78 | 36           | 0.2391 | 0.9589                         | 0.8109                          | 0.4979                         | 0.8711                                |
| 208768 x at             | 0.30          | 14.56 | 0.05 | 12.78 | 37           | 0.2858 | 0.9577                         | 0.8867                          | 0.4568                         | 0.9964                                |
| 212191 x at             | 0.18          | 14.84 | 0.05 | 12.77 | 38           | 0.2500 | 0.9777                         | 0.8542                          | 0.3553                         | 0.9844                                |
| 200021 at               | 0.50          | 13.77 | 0.02 | 12.77 | 39           | 0.2775 | 0.8529                         | 0.8339                          | 0.5283                         | 0.2775                                |
| 208517 x at             | 0.33          | 14.54 | 0.02 | 12.56 | 40           | 0.2513 | 0.7046                         | 0.7417                          | 0.9434                         | 0.2954                                |
| 211956 s at             | 0.16          | 15.12 | 0.08 | 12.50 | 41           | 0.2756 | 0.2756                         | 0.3283                          | 0.6567                         | 0.4596                                |
| 214351 x at             | 0.44          | 14.01 | 0.03 | 12.36 | 42           | 0.2703 | 0.4829                         | 0.9230                          | 0.9173                         | 0.4119                                |
| 224731 at               | 0.11          | 14.37 | 0.17 | 12.35 | 43           | 0.3496 | 0.4679                         | 0.9363                          | 0.4219                         | 0.3496                                |
| 234512 x at             | 0.25          | 13.55 | 0.04 | 12.35 | 44           | 0.5910 | 0.9435                         | 0.5910                          | 0.9578                         | 0.6021                                |
| 220960 x at             | 0.28          | 14.20 | 0.02 | 12.28 | 45           | 0.5585 | 0.7556                         | 0.8571                          | 0.7995                         | 0.9640                                |
| 221791 s at             | 0.45          | 14.33 | 0.03 | 12.22 | 46           | 0.2692 | 0.5460                         | 0.8746                          | 0.4059                         | 0.2692                                |
| 216438 s at             | 0.04          | 15.34 | 1.15 | 12.02 | 47           | 0.2086 | 0.3130                         | 0.2155                          | 0.2086                         | 0.8821                                |
| 201030 x at             | 0.22          | 14.68 | 0.05 | 11.91 | 48           | 0.3032 | 0.4740                         | 0.8098                          | 0.5684                         | 0.3032                                |
| AFFX-CreX-<br>3 at      | 0.27          | 14.50 | 0.19 | 11.83 | 49           | 0.4700 | 0.9276                         | 0.5873                          | 0.7234                         | 0.9267                                |
| 200715 x at             | 0.26          | 13.87 | 0.12 | 11.70 | 50           | 0.3000 | 0.8556                         | 0.3818                          | 0.6143                         | 0.4458                                |
| AFFX-CreX-<br>5 at      | 0.15          | 14.64 | 0.27 | 11.59 | 51           | 0.3900 | 0.9872                         | 0.6546                          | 0.5814                         | 0.7754                                |
| 222976 s at             | 0.04          | 14.13 | 0.09 | 11.54 | 52           | 0.3646 | 0.3786                         | 0.7883                          | 0.3646                         | 0.5240                                |
| 210466 s at             | 0.52          | 13.90 | 0.07 | 11.51 | 53           | 0.2326 | 0.3230                         | 0.2326                          | 0.2545                         | 0.8323                                |
| 225413 at               | 0.07          | 13.78 | 0.15 | 11.49 | 54           | 0.3239 | 0.9696                         | 0.5515                          | 0.8338                         | 0.3239                                |

| Probe        | VarW.<br>VarB | mean  | var  | vscr. | vscr.<br>rank | P.Min  | SCR.<br>anti-<br>CD40.<br>Ab.1 | IC25.<br>anti-<br>CD40.<br>Ab.1 | GCB.<br>anti-<br>CD40.<br>Ab.1 | SCR<br>EXT.<br>anti-<br>CD40.<br>Ab.1 |
|--------------|---------------|-------|------|-------|---------------|--------|--------------------------------|---------------------------------|--------------------------------|---------------------------------------|
| 221691 x at  | 0.10          | 15.00 | 0.07 | 11.44 | 55            | 0.5097 | 0.8965                         | 0.7627                          | 0.5097                         | 0.7686                                |
| 229353 s at  | 0.07          | 13.62 | 0.21 | 11.21 | 56            | 0.6703 | 0.7457                         | 0.6703                          | 0.7602                         | 0.8020                                |
| 1555730 a at | 0.04          | 14.01 | 0.30 | 11.17 | 57            | 0.4996 | 0.9337                         | 0.7560                          | 0.4996                         | 0.5768                                |
| 200966 x at  | 0.09          | 14.02 | 0.11 | 11.09 | 58            | 0.2409 | 0.2409                         | 0.5526                          | 0.4352                         | 0.8701                                |
| 224654 at    | 0.06          | 13.50 | 0.13 | 11.07 | 59            | 0.6759 | 0.8439                         | 0.8720                          | 0.7694                         | 0.6759                                |
| 224944 at    | 0.05          | 13.48 | 0.14 | 10.98 | 60            | 0.2455 | 0.3257                         | 0.4478                          | 0.3876                         | 0.2455                                |
| 222985 at    | 0.04          | 13.53 | 0.15 | 10.86 | 61            | 0.3506 | 0.7800                         | 0.3506                          | 0.9581                         | 0.9505                                |
| 1555837 s at | 0.07          | 13.18 | 0.16 | 10.85 | 62            | 0.3371 | 0.8399                         | 0.3612                          | 0.6857                         | 0.3371                                |
| 209026 x at  | 0.07          | 13.60 | 0.24 | 10.73 | 63            | 0.2100 | 0.6957                         | 0.4642                          | 0.7072                         | 0.3910                                |
| 238199 x at  | 0.56          | 11.52 | 0.17 | 10.69 | 64            | 0.2720 | 0.3736                         | 0.9156                          | 0.2720                         | 0.6534                                |
| 217807 s at  | 0.07          | 13.62 | 0.19 | 10.61 | 65            | 0.5757 | 0.8314                         | 0.7256                          | 0.7767                         | 0.5757                                |
| 242131 at    | 0.53          | 11.20 | 0.10 | 10.42 | 66            | 0.5733 | 0.7746                         | 0.5733                          | 0.7302                         | 0.9388                                |
| 222980 at    | 0.12          | 12.27 | 0.13 | 10.40 | 67            | 0.2461 | 0.7382                         | 0.9132                          | 0.2877                         | 0.2461                                |
| 234339 s at  | 0.58          | 11.32 | 0.29 | 10.39 | 68            | 0.6277 | 0.7136                         | 0.9772                          | 0.8445                         | 0.6277                                |
| 1554678 s at | 0.04          | 13.21 | 0.22 | 10.39 | 69            | 0.3095 | 0.3381                         | 0.3095                          | 0.6767                         | 0.5390                                |
| 200893 at    | 0.12          | 13.68 | 0.06 | 10.38 | 70            | 0.3885 | 0.5944                         | 0.8186                          | 0.6001                         | 0.3885                                |
| 223105 s at  | 0.02          | 13.54 | 0.16 | 10.35 | 71            | 0.6699 | 0.6699                         | 0.8055                          | 0.8667                         | 0.9663                                |
| 224579 at    | 0.02          | 13.49 | 0.20 | 10.21 | 72            | 0.2496 | 0.7799                         | 0.3541                          | 0.3506                         | 0.2496                                |
| 1558678 s at | 0.16          | 12.46 | 0.89 | 10.21 | 73            | 0.4393 | 0.9362                         | 0.8914                          | 0.4393                         | 0.9347                                |
| 223096 at    | 0.03          | 13.04 | 0.13 | 10.13 | 74            | 0.6162 | 0.6964                         | 0.8240                          | 0.6162                         | 0.6685                                |
| 224567 x at  | 0.11          | 12.50 | 0.69 | 10.10 | 75            | 0.4566 | 0.9218                         | 0.9662                          | 0.4566                         | 0.7071                                |
| 226385 s at  | 0.03          | 12.99 | 0.26 | 10.02 | 76            | 0.6285 | 0.6285                         | 0.9109                          | 0.7478                         | 0.8336                                |
| 213011 s at  | 0.04          | 13.56 | 0.18 | 9.96  | 77            | 0.2442 | 0.3471                         | 0.6334                          | 0.5709                         | 0.4333                                |
| 225892 at    | 0.10          | 12.08 | 0.21 | 9.94  | 78            | 0.4034 | 0.8084                         | 0.9066                          | 0.6860                         | 0.4034                                |
| 231896 s at  | 0.03          | 12.80 | 0.14 | 9.93  | 79            | 0.2977 | 0.6041                         | 0.7701                          | 0.2977                         | 0.4713                                |
| 201114 x at  | 0.12          | 12.78 | 0.15 | 9.87  | 80            | 0.4093 | 0.5862                         | 0.5983                          | 0.8588                         | 0.4093                                |

| Probe                    | symb     | VarW.<br>VarB | mean  | var  | vscr | vscr.<br>rank | P.Min  | SCR.<br>anti-<br>CD40.<br>Ab.1 | IC25.<br>anti-<br>CD40.<br>Ab.1 | GCB.<br>anti-<br>CD40.<br>Ab.1 | SCR<br>EXT.<br>anti-<br>CD40.<br>Ab.1 |
|--------------------------|----------|---------------|-------|------|------|---------------|--------|--------------------------------|---------------------------------|--------------------------------|---------------------------------------|
| 208738 x at              | SUMO2    | 0.17          | 14.07 | 0.02 | 9.87 | 81            | 0.2055 | 0.4579                         | 0.4606                          | 0.3408                         | 0.2055                                |
| 224592 x at              | HP1BP3   | 0.13          | 11.74 | 0.15 | 9.86 | 82            | 0.6319 | 0.6899                         | 0.6319                          | 0.8361                         | 0.8069                                |
| 224935 at                | EIF2S3   | 0.03          | 13.01 | 0.35 | 9.86 | 83            | 0.2694 | 0.3291                         | 0.6816                          | 0.2694                         | 0.3207                                |
| 224736 at                | CCAR1    | 0.10          | 11.79 | 0.09 | 9.86 | 84            | 0.5647 | 0.8733                         | 0.9743                          | 0.7364                         | 0.5647                                |
| 224593 at                | ZNF664   | 0.20          | 11.63 | 0.37 | 9.85 | 85            | 0.4300 | 0.5453                         | 0.8490                          | 0.4300                         | 0.9881                                |
| 224714 at                | MKI67IP  | 0.07          | 12.26 | 0.23 | 9.83 | 86            | 0.3898 | 0.8170                         | 0.7194                          | 0.3898                         | 0.5026                                |
| 223705 s at              | GPBP1    | 0.05          | 12.26 | 0.12 | 9.79 | 87            | 0.6059 | 0.9591                         | 0.9834                          | 0.6059                         | 0.9781                                |
| 1553575 at               | NA       | 0.04          | 12.71 | 0.40 | 9.76 | 88            | 0.2247 | 0.3970                         | 0.3953                          | 0.2247                         | 0.4525                                |
| 224591 at                | HP1BP3   | 0.04          | 12.57 | 0.24 | 9.72 | 89            | 0.6293 | 0.6293                         | 0.6998                          | 0.7775                         | 0.9947                                |
| 202690 s at              | SNRPDI   | 0.07          | 13.90 | 0.13 | 9.70 | 90            | 0.5018 | 0.7715                         | 0.5905                          | 0.5018                         | 0.5865                                |
| 223034 s at              | C1orf43  | 0.02          | 13.12 | 0.16 | 9.70 | 91            | 0.4517 | 0.6653                         | 0.4517                          | 0.7044                         | 0.9095                                |
| 224376 s at              | C20orf24 | 0.06          | 12.21 | 0.23 | 9.69 | 92            | 0.5630 | 0.9644                         | 0.9137                          | 0.8592                         | 0.5630                                |
| AFFX-r2-Ec-<br>bioD-3 at | NA       | 0.14          | 14.01 | 0.48 | 9.67 | 93            | 0.3700 | 0.8588                         | 0.8057                          | 0.4071                         | 0.4774                                |
| 201277 s at              | HNRPAB   | 0.04          | 13.17 | 0.18 | 9.66 | 94            | 0.3203 | 0.8462                         | 0.3900                          | 0.3789                         | 0.3203                                |
| 228273 at                | NA       | 0.03          | 12.65 | 0.19 | 9.66 | 95            | 0.5447 | 0.5447                         | 0.6935                          | 0.9994                         | 0.8749                                |
| 202077 at                | NDUFAB1  | 0.06          | 13.06 | 0.08 | 9.65 | 96            | 0.2839 | 0.9323                         | 0.6388                          | 0.6981                         | 0.2839                                |
| 224561 s at              | MORF4L1  | 0.04          | 12.46 | 0.18 | 9.64 | 97            | 0.6517 | 0.9637                         | 0.6517                          | 0.8271                         | 0.7722                                |
| 211623 s at              | FBL      | 0.04          | 13.89 | 0.16 | 9.63 | 98            | 0.4800 | 0.5149                         | 0.9574                          | 0.8996                         | 0.9424                                |
| 212626 x at              | HNRPC    | 0.08          | 13.05 | 0.14 | 9.62 | 99            | 0.2260 | 0.5906                         | 0.5146                          | 0.3161                         | 0.4689                                |
| 229128 s at              | ANP32E   | 0.03          | 12.72 | 0.39 | 9.61 | 100           | 0.4422 | 0.6538                         | 0.8542                          | 0.4422                         | 0.9196                                |

Table 9.

| Probe        | sybm.gse  | VarW.<br>VarB | mean  | var  | vscr  | vscr.<br>rank | P.Min  | SCR.<br>anti-<br>CD40 | IC25.<br>anti-<br>CD40 | GCB.<br>anti-<br>CD40 | SCR<br>EXT.<br>anti-<br>CD40 |
|--------------|-----------|---------------|-------|------|-------|---------------|--------|-----------------------|------------------------|-----------------------|------------------------------|
| 226131 s at  | RPS16     | 0.68          | 15.60 | 0.01 | 15.24 | 1             | 0.4182 | 0.6946                | 0.6783                 | 0.9425                | 0.4182                       |
| 1553567 s at | ATP13A5   | 0.53          | 15.77 | 0.04 | 15.10 | 2             | 0.2744 | 0.3205                | 0.5881                 | 0.2744                | 0.8039                       |
| 213477 x at  | EEF1A1    | 0.80          | 15.71 | 0.02 | 14.94 | 3             | 0.2716 | 0.3490                | 0.5611                 | 0.2716                | 0.9425                       |
| 211542 x at  | RPS10     | 0.59          | 15.11 | 0.02 | 14.31 | 9             | 0.2000 | 0.8313                | 0.9604                 | 0.7117                | 0.7029                       |
| 200095 x at  | FLJ20294  | 0.60          | 15.29 | 0.02 | 13.98 | 12            | 0.3400 | 0.7334                | 0.5003                 | 0.4045                | 0.4757                       |
| 224585 x at  | ACTG1     | 0.49          | 14.73 | 0.06 | 13.96 | 13            | 0.4788 | 0.9612                | 0.7590                 | 0.4788                | 0.5097                       |
| 213414 s at  | RPS19     | 0.49          | 15.19 | 0.02 | 13.95 | 14            | 0.3134 | 0.6110                | 0.5909                 | 0.3134                | 0.9180                       |
| 200032 s at  | RPL9      | 0.61          | 15.30 | 0.01 | 13.80 | 16            | 0.2652 | 0.7969                | 0.6658                 | 0.8910                | 0.9033                       |
| 200063 s at  | NPM1      | 0.68          | 15.34 | 0.02 | 13.78 | 17            | 0.2634 | 0.6557                | 0.7122                 | 0.2634                | 0.9201                       |
| 212734 x at  | RPL13     | 0.46          | 14.92 | 0.03 | 13.66 | 19            | 0.2300 | 0.8232                | 0.6720                 | 0.4503                | 0.7004                       |
| 200689 x at  | EEF1G     | 0.64          | 14.25 | 0.03 | 13.21 | 26            | 0.2100 | 0.9324                | 0.8163                 | 0.8508                | 0.3667                       |
| 200024 at    | RPS5      | 0.57          | 14.61 | 0.03 | 13.09 | 31            | 0.2000 | 0.7753                | 0.8060                 | 0.5846                | 0.9469                       |
| 200003 s at  | RPL28     | 0.14          | 15.12 | 0.04 | 12.93 | 34            | 0.5687 | 0.9905                | 0.6582                 | 0.9539                | 0.5687                       |
| 221775 x at  | EV11      | 0.28          | 14.55 | 0.05 | 12.78 | 36            | 0.2391 | 0.9589                | 0.8109                 | 0.4979                | 0.8711                       |
| 208768 x at  | RPL22     | 0.30          | 14.56 | 0.05 | 12.78 | 37            | 0.2858 | 0.9577                | 0.8867                 | 0.4568                | 0.9964                       |
| 212191 x at  | LOC388344 | 0.18          | 14.84 | 0.05 | 12.77 | 38            | 0.2500 | 0.9777                | 0.8542                 | 0.3553                | 0.9844                       |
| 200021 at    | CFL1      | 0.50          | 13.77 | 0.02 | 12.77 | 39            | 0.2775 | 0.8529                | 0.8339                 | 0.5283                | 0.2775                       |
| 208517 x at  | BTF3      | 0.33          | 14.54 | 0.02 | 12.56 | 40            | 0.2513 | 0.7046                | 0.7417                 | 0.9434                | 0.2954                       |
| 211956 s at  | EIF1      | 0.16          | 15.12 | 0.08 | 12.50 | 41            | 0.2756 | 0.2756                | 0.3283                 | 0.6567                | 0.4596                       |
| 224731 at    | HMGB1     | 0.11          | 14.37 | 0.17 | 12.35 | 43            | 0.3496 | 0.4679                | 0.9363                 | 0.4219                | 0.3496                       |
| 234512 x at  | LOC388474 | 0.25          | 13.55 | 0.04 | 12.35 | 44            | 0.5910 | 0.9435                | 0.5910                 | 0.9578                | 0.6021                       |
| 221791 s at  | CCDC72    | 0.45          | 14.33 | 0.03 | 12.22 | 46            | 0.2692 | 0.5460                | 0.8746                 | 0.4059                | 0.2692                       |
| 216438 s at  | TMSB4X    | 0.04          | 15.34 | 1.15 | 12.02 | 47            | 0.2086 | 0.3130                | 0.2155                 | 0.2086                | 0.8821                       |
| 201030 x at  | LDHB      | 0.22          | 14.68 | 0.05 | 11.91 | 48            | 0.3032 | 0.4740                | 0.8098                 | 0.5684                | 0.3032                       |
| 222976 s at  | TPM3      | 0.04          | 14.13 | 0.09 | 11.54 | 52            | 0.3646 | 0.3786                | 0.7883                 | 0.3646                | 0.5240                       |

| Probe       | symb.gse | Var W.<br>Var B | mean  | var  | vscr  | vscr.<br>rank | P.Min  | SCR.<br>anti-<br>CD40 | IC25.<br>anti-<br>CD40 | GCB.<br>anti-<br>CD40 | SCR<br>EXT.<br>anti-<br>CD40 |
|-------------|----------|-----------------|-------|------|-------|---------------|--------|-----------------------|------------------------|-----------------------|------------------------------|
| 210466 s at | SERBP1   | 0.52            | 13.90 | 0.07 | 11.51 | 53            | 0.2326 | 0.3230                | 0.2326                 | 0.2545                | 0.8323                       |
| 225413 at   | USMG5    | 0.07            | 13.78 | 0.15 | 11.49 | 54            | 0.3239 | 0.9696                | 0.5515                 | 0.8338                | 0.3239                       |
| 221691 x at | NPM1     | 0.10            | 15.00 | 0.07 | 11.44 | 55            | 0.5097 | 0.8965                | 0.7627                 | 0.5097                | 0.7686                       |

Measuring expression level

[0092] The methods disclosed herein provide methods to examine expression level of one or more of these marker genes in a lymphoma sample (*e.g.*, B-cell lymphoma sample) relative a reference level. The methods and assays include those which examine expression of marker genes such as one or more of those listed in any of Tables 2-4, 6, 7 and 13.

Expression levels may be measured at mRNA level and/or protein level.

[0093] 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.

[0094] 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 not limited to, microarray (gene and/or tissue array analysis), *in situ* hybridization, Northern analysis, PCR analysis of mRNAs, immunohistochemical and/or Western analysis, 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 those listed in Tables 2-4, 6, 7 and 13, in a sample are provided for illustrative purposes.

[0095] In some embodiments, the methods of the invention further include protocols which examine the presence and/or expression of mRNAs, such as mRNAs of genes listed in any of Tables 2-4, 6, 7 and 13, 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, such as mRNAs in any of Tables 2-4, 6, 7 and 13, 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).

**[0096]** 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.

**[0097]** 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 listed in any of Tables 2-4, 6, 7 and 13.

**[0098]** 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 listed in any of Tables 2-4, 6, 7 and 13, and other amplification type detection methods, such as, for example, branched DNA, SISBA, TMA and the like).

**[0099]** Tissue or cell samples from mammals can be conveniently assayed for, *e.g.*, mRNAs of genes listed in any of Tables 2-4, 6, 7 and 13, 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, the RT-PCR may be quantitative RT-PCR (qRT-PCR). In some embodiments, the RT-PCR is real-time RT-PCR. In some embodiments, the 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, the real-time RT-PCR may be quantitative RT-PCR. In some embodiments, the real-time RT-PCR may be performed using TaqMan® chemistry (Applied Biosystems). In some embodiments, the real-time RT-PCR may be performed using TaqMan® chemistry (Applied Biosystems) and the ABI Prism® 7700 Sequence Detection System (Applied Biosystems). The 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, such as a mRNA of genes listed in any of Tables 2-4, 6, 7 and 13, 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 Table 8 or Table 9). Examples of primers and probes that may be used for conducting qRT-PCR are provided in Table 10.

**[0100]** In some embodiments, the expression of proteins encoded by the genes listed in any of Tables 2-4, 6, 7 and 13 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.

[0101] 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.

[0102] 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,” 3<sup>rd</sup> 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.

[0103] 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, Broid, 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.

[0104] 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.

[0105] 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 one or more genes listed in Tables 1-4, 6 and 7) 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.

[0106] 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  $^{35}\text{S}$ ,  $^{14}\text{C}$ ,  $^{125}\text{I}$ ,  $^3\text{H}$ , and  $^{131}\text{I}$ . 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,  $\beta$ -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).

**[0107]** 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)  $\beta$ -D-galactosidase ( $\beta$ -D-Gal) with a chromogenic substrate (*e.g.*, p-nitrophenyl- $\beta$ -D-galactosidase) or fluorogenic substrate (*e.g.*, 4-methylumbelliferyl- $\beta$ -D-galactosidase).

**[0108]** 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.

**[0109]** 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)).

**[0110]** 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).

**[0111]** 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 genes listed in any of Tables 2-4, 6 and 7. 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.

**[0112]** 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+ |

**[0113]** 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.

**[0114]** 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.

**[0115]** 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.

**[0116]** 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.

**[0117]** 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.

**[0118]** 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.

**[0119]** 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.

[0120] 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.

[0121] 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*

[0122] 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.

[0123] 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 (*e.g.*, genes in Table 8 or Table 9). 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.

[0124] 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). 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. See Table 4 for marker genes having increased and decreased expression in anti-CD40 antibody sensitive cells as compared to resistant cells. For examples, VNN2, MEF2C, LTB, KCNN3, NCF1, BCL6, IGJ, ELTI1902, PNOC, CSF2RB, POU2AF1, CD22, RGS13, and MEF2B are generally overexpressed in anti-CD40 antibody sensitive cells as compared to resistant cells. 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.

**[0125]** In some embodiments, 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, and PUS7 are compared to a reference level.

**[0126]** 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.

**[0127]** 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.

**[0128]** 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 2, 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.

**[0129]** In some embodiments, the expression levels of marker genes in Table 7) are measured, and a sensitivity index calculated as the sum of signed t-scores for log2-scale expression of genes pairs 1-8 in Table 7 is determined, wherein a sensitivity index greater than -4 suggests or indicates the B-cell lymphoma is responsive to an anti-CD40 antibody treatment. In some embodiments, the sensitivity index is greater than -3, greater than -2, greater than -1, or greater than 0. In some embodiments, the sensitivity index is between -4 and 20. In some embodiments, the sensitivity index is between 0 and 20.

**[0130]** In some embodiments, the expression levels of one or more of IFITM1, CD40, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7 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 13 are measured; wherein (i)  $\beta_j$  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 expression level of each marker measured; and (iv)  $\mu_j$  and  $\sigma_j$  are means and standard deviations for each marker gene measured; wherein  $\beta_j$ ,  $\mu_j$  and  $\sigma_j$  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. Example 2 described in detail how to analyze and determine parameters for reference samples and new samples. 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, equal number of positive correlated marker genes and negative correlated marker genes are measured and used for the sensitivity index calculation.

[0131] 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.

[0132] The comparison can be carried out in any convenient manner appropriate to the type of measured value and reference value for the gene markers at issue. The process of comparing may be manual or it may be automatic. 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 2. 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

[0133] 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.

**[0134]** 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 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.

**[0135]** 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.

**[0136]** 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.

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[0137] 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.

[0138] 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.

In some embodiments,

the anti-CD40 antibody for used 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  $1 \times 10^{-8}$  or no higher than  $1 \times 10^{-9}$ . 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.

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

[0139] 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.

**[0140]** 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 listed in Table 1-4, 6, 7 and 13, in a sample and as a means for detecting a cell expressing proteins encoded by the polynucleotides corresponding to genes listed in Table 1-4, 6, 7 and 13. As will be understood by the skilled artisan, a great many different primers and probes may be prepared based on the sequences provided in herein and used effectively to amplify, clone and/or determine the presence and/or levels of mRNAs.

**[0141]** In some embodiments, the kits comprise reagents for detecting expression levels of at least two, at least three, at least five, at least ten, at least fifteen, at least twenty marker genes. Kits may also comprise reference samples that are useful as generating reference values. The marker genes include, but are not limited to VNN2, MEF2C, LTB, KCNN3, NCF1, BCL6, IGJ, ELTI1902, PNOC, CSF2RB, POU2AF1, CD22, RGS13, MEF2B, LRRC8A, CD40, IFITM1, SMN1, PRRCA, EPDR1, PRPSAP2, IGF1R, BTG2, LMO2, YIPF3, CD79B, CD44, CTSC, UAP1, and PUS7. 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.

**[0142]** In some embodiments, the kits comprises 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 10. 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.

**[0143]** The reagents for detecting protein expression level of a marker gene may comprise an antibody that specifically binds to the protein encoded by the marker gene.

**[0144]** 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.

[0145] 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.

[0146] The kit can further comprise a set of instructions and materials for preparing a tissue or cell sample and preparing nucleic acid (such as mRNA) from the sample.

[0147] 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.

[0148] 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](http://cmt.corning.com) and [cmgm.stanford.edu/pbrown1](http://cmgm.stanford.edu/pbrown1).

[0149] 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.

[0150] 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 predictive genetic markers for responsiveness of NHL patients to anti-CD40 antibody treatment**

##### **Materials and Methods**

###### *Cell Viability assays*

[0151] NHL Cells were seeded in 384 well plates at 1500-5000 cells/well in 50ul RPMI 1640 supplemented with 2% FBS and treated with serial concentrations of crosslinked anti-CD40 Ab.1 or control antibody (anti-gD 5B6). For crosslinking, anti-CD40 Ab.1 or anti-gD was incubated with F(ab')<sub>2</sub> fragments of a goat anti human IgG Fc $\gamma$  fragment-specific antibody (Jackson ImmunoResearch, West Grove, PA) in a 1:4 ratio in medium for 30 minutes at room temperature before adding to cells. After 96 hours of incubation, cell viability was evaluated using CellTiter-Glo Luminescent Cell Viability Assay (Promega, Madison, WI) according to the manufacturer's instructions. Each data point was performed in quadruplicate.

[0152] XLfit was used to calculate IC<sub>50</sub>, IC<sub>25</sub> and maximum inhibition. Data are expressed as average of three independent experiments. Sensitivity to anti-CD40 Ab.1 was binned into three categories: Sensitive, Intermediate, and Resistant based on IC<sub>25</sub> and IC<sub>50</sub> values.

###### *Antibody*

[0153] anti-CD40 Ab.1 is a humanized IgG1 mAb against CD40. It is produced in and secreted by a genetically engineered Chinese Hamster Ovary (CHO) cell line. The anti-CD40 Ab.1 used in the examples and referred to as anti-CD40 Ab.1 has the following amino acid sequence:

[0154] *Heavy Chain* (SEQ ID NO:1). The italicized underlined ASN 294 residue identifies the location of the carbohydrate moiety.

69790-82

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

[0155] *Light Chain* (SEQ ID NO:2).

|                                                        |     |
|--------------------------------------------------------|-----|
| DIQMTQSPSS LSASVGDRTV ITCRSSQSLV HSNNGTFLHW YQKPGKAPK  | 50  |
| LLIYTVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YFCSQTHVP  | 100 |
| WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK | 150 |
| VQWKVDNALQ SGNSQESVTE QDSKDYSTSL SSTLTLSKAD YEKHKVYACE | 200 |
| VTHQGLSSPV TKSFNREGC                                   | 219 |

*Generation and analysis of gene expression profiles*

[0156] Total RNA was extracted with the *mirVana*<sup>TM</sup> miRNA Isolation Kit (Ambion, Austin, TX) and was assayed using Affymetrix HGU133P2 whole genome expression microarrays. Raw data was extracted using an Affymetrix scanner and the resulting CEL files were processed using gcRMA with defaults in R Bioconductor Package (world wide web at [bioconductor.org](http://bioconductor.org)). Significantly differentially expressed genes were identified using a moderated t-test for differences across anti-CD40 Ab.1 sensitivity and viability classes. Further parameters were assessed using the LIMA package and t-statistics, p-values, adjusted p-values, and B-statistics were calculated for each gene. Probes were mapped to each gene and a 1:1 probe to gene mapping was selected for downstream analysis using the probe most strongly associated with the measure of sensitivity. For classification into Sensitive or Intermediate versus Resistant groups, quantitative stepwise linear modeling was combined with qualitative analysis of target pathways to identify a parsimonious set of genes to inclusion in the assay. Further details and results are provided in the Results (Table 7).

[0157] Gene set enrichment analysis was determined by utilizing the GSEA module within Gene Pattern (Reich et al. Gene Pattern 2.0 Nature Genetics 38 no. 5 (2006) pp 500-501). The enrichment score awards pre-specified classes of genes when their members are significantly differentially expressed in a concordant manner across phenotypes. The normalized enrichment score is calculated by taking the enrichment score and adjusting for the number of genes within a gene set. The nominal p-value is determined by permutating the sensitive and resistant labels and recomputing the normalized enrichment score to give a null distribution.

*anti-CD40 Ab.1 Sensitivity Index Identified Using Stepwise Linear Modeling*

[0158] Each Target Gene is shown with its corresponding inversely correlated (anti-correlated) Pair Gene (Table 7), in order of the step at which the Target Gene was chosen for inclusion in the Index. The first 3 Main Genes (VNN2, RGS13, CD22 in Table 7) were selected from Tables 2-4 (Step 1) to model the dominant component of differential over-expression in Sensitive and Intermediate cell lines. The expression of these 3 genes is highly correlated, with correlation coefficients of +0.77 or higher. Due to their similarity, a single pair gene EPDR1 was selected from Tables 2-4 to measure contrasting overexpression in Resistant cell lines. Including such anti-correlated Pair Genes in the assay provides auto-normalization in that both Sensitivity and Resistance are associated with high expression of one arm of the pair. By this mechanism, the assay does not depend upon low overall mRNA assay levels to define any class, but rather describes each by a pattern of relative expression of the Main Genes to their anticorrelated Pairs (i.e. a sum of signed t-scores on the log<sub>2</sub> scale, with signs corresponding to the Fold Change Estimate). In Steps 2-5, additional pairs of genes were chosen based upon mechanism of action from a new list of those with significant associations to IC25 after adjustment for the cumulative sum of signed t-scores for genes identified in previous Steps. This stepwise procedure requires each new pair of genes to add additional predictive power to the Sensitivity Index. After Step 5, no more gene pairs were needed for IC25 prediction. In Step 6, a single additional pair was added for its ability to predict cell viability at maximum inhibition after adjusting for the cumulative Index based upon the previous 7 pairs of genes. BCL6 was added as a singleton without a corresponding pair based upon a mechanism of action rationale: it is not currently incorporated in the final Sensitivity Index, which is given by the sum of signed t-scores for log<sub>2</sub>-scale expression of Gene Pairs 1-8. It may be incorporated explicitly into the index based upon clinical experience. For classification into Sensitive or Intermediate versus Resistant groups, a preliminary cutoff was chosen for the Sensitivity Index so as to maximize the overall correct classification rate. Alternate classification rules based upon the selected probes may be optimized later for clinical application.

**Results and Analysis**

[0159] To gain an understanding of the mechanism of action of anti-CD40 antibody, and to identify one or more predictive markers for the responsiveness of NHL patients to anti-CD40 antibody therapy, we tested the activity of anti-CD40 Ab.1 across a panel of 31 NHL cell

lines and assessed cell viability in response to a titration of anti-CD40 antibody. The IC25 values highlighted in Table 1 from this experiment reveal that anti-CD40 antibody sensitized 10 cell lines with a reduction in cell viability at a concentration of <0.4 µg/ml, hereon defined as 'sensitive' cell lines, and 13 cell lines that did not achieve a reduction in cell viability even up to concentrations of 1 µg/ml, hereon defined as 'resistant' cell lines. 8 cell lines had an IC25 between >0.4 and <0.8, and will hereon be defined as 'intermediate' cell lines.

[0160] Table 1 provides anti-CD40 Ab.1 IC25 sensitivity data across NHL cell lines in vitro. Specific lymphoma subtypes of each cell line, IC25 values and classifier data are given for each cell line. DLBCL (Diffuse Large B-cell Lymphoma), FL (Follicular Lymphoma), MCL (Mantle Cell Lymphoma), ALCL (Anaplastic Large Cell Lymphoma).

Table 1.

| Cell line    | Anti-CD40 Antibody Sensitivity IC25 Classifier | Anti-CD40 Antibody IC25 (µg/ml) | Lymphoma Subtype   |
|--------------|------------------------------------------------|---------------------------------|--------------------|
| SU-DHL-16    | Sensitive                                      | 0.009817124                     | DLBCL              |
| SU-DHL-10    | Sensitive                                      | 0.01                            | DLBCL              |
| SU-DHL-8     | Sensitive                                      | 0.011140955                     | DLBCL              |
| SU-DHL-5     | Sensitive                                      | 0.015309599                     | DLBCL              |
| SU-DHL-4     | Sensitive                                      | 0.03                            | DLBCL              |
| MC116        | Sensitive                                      | 0.03217012                      | UBCL               |
| HT           | Sensitive                                      | 0.123333333                     | DLBCL              |
| KARPAS-1106P | Sensitive                                      | 0.196666667                     | DLBCL              |
| BJAB         | Sensitive                                      | 0.240995143                     | Burkitt's Lymphoma |
| WSU-NHL      | Sensitive                                      | 0.348838607                     | FL                 |
| REC-1        | Intermediate                                   | 0.42                            | MCL                |
| WSU-FSCCL    | Intermediate                                   | 0.49                            | FL                 |
| A3/Kawakami  | Intermediate                                   | 0.668463355                     | DLBCL              |
| DB           | Intermediate                                   | 0.676933804                     | DLBCL              |
| Ri-1         | Intermediate                                   | 0.696666667                     | DLBCL              |
| RL           | Intermediate                                   | 0.698508885                     | DLBCL              |
| Sc-1         | Intermediate                                   | 0.709276746                     | FL                 |
| Farage       | Intermediate                                   | 0.796666667                     | DLBCL              |
| A4/Fukada    | Resistant                                      | 1                               | DLBCL              |
| GRANTA-519   | Resistant                                      | 1                               | MCL                |
| JeKo-1       | Resistant                                      | 1                               | MCL                |
| Karpas-422   | Resistant                                      | 1                               | DLBCL              |
| NU-DHL-1     | Resistant                                      | 1                               | DLBCL              |
| OCI-Ly19     | Resistant                                      | 1                               | DLBCL              |
| Pfeiffer     | Resistant                                      | 1                               | DLBCL              |
| RC-K8        | Resistant                                      | 1                               | DLBCL              |

| Cell line | Anti-CD40 Antibody Sensitivity IC25 Classifier | Anti-CD40 Antibody IC25 ( $\mu\text{g/ml}$ ) | Lymphoma Subtype |
|-----------|------------------------------------------------|----------------------------------------------|------------------|
| SCC-3     | Resistant                                      | 1                                            | DLBCL            |
| SR-786    | Resistant                                      | 1                                            | ALCL             |
| SU-DHL-1  | Resistant                                      | 1                                            | ALCL             |
| TK        | Resistant                                      | 1                                            | DLBCL            |
| Toledo    | Resistant                                      | 1                                            | DLBCL            |

[0161] To identify genes that are predictive of anti-CD40 Ab.1 activity in vitro, RNA was prepared from the cell lines at the log stage of cell division and subjected to gene expression profiling using the Affymetrix HGU133P2 microarray. Differentially expressed genes between Sensitive and Resistant cell lines were determined by a moderated t-test and significance was determined using an adjusted P-value cutoff of  $\leq 0.05$  (Table 2). In Table 2, gene list filtered to an adjusted p-value  $< 0.05$  (5% FDR) resulting in 110 unique genes. Probe ID, gene symbol and description are indicated. In addition, significant genes that correlated with the IC25 values across all NHL cell lines were determined by the Spearman's Rank Correlation and genes were filtered using a rho value of  $\leq -0.57$  or  $\geq 0.57$  (Table 3). In Table 3, gene list filtered with a rho value of  $\leq -0.57$  or  $\geq 0.57$  resulting in 130 unique genes. Probe ID, gene symbol and description are also indicated. A combined table of unique genes identified by each or both methodologies is displayed in Table 4. In Table 4, the Log(2) fold change is indicated where a positive fold change represents increased expression in the sensitive class and a negative fold change represents increased expression in the resistant class of NHL cell lines with respect to anti-CD40 Ab.1 sensitivity. Gene represents 195 unique genes. Probe IDs, gene symbol and description are also indicated.

Table 2.

| Gene Symbol | Probe        | Description                                                                          | adj.P.Val   |
|-------------|--------------|--------------------------------------------------------------------------------------|-------------|
| RGS13       | 210258_at    | regulator of G-protein signalling 13                                                 | 2.57E-05    |
| MGC2463     | 219812_at    |                                                                                      | 0.00015799  |
| VNN2        | 205922_at    | vanin 2                                                                              | 0.000247994 |
| EPDR1       | 223253_at    | ependymin related protein 1 (zebrafish)                                              | 0.000434413 |
| MEF2B       | 205124_at    | MADS box transcription enhancer factor 2, polypeptide B (myocyte enhancer factor 2B) | 0.001352572 |
| SLAMF6      | 1552497_a_at | SLAM family member 6                                                                 | 0.00263509  |
| LCK         | 204891_s_at  | lymphocyte-specific protein tyrosine kinase                                          | 0.00263509  |

| Gene Symbol | Probe        | Description                                                                                                      | adj.P.Val   |
|-------------|--------------|------------------------------------------------------------------------------------------------------------------|-------------|
| LPP         | 202822_at    | LIM domain containing preferred translocation partner in lipoma                                                  | 0.005668066 |
| SLC30A1     | 212907_at    | solute carrier family 30 (zinc transporter), member 1                                                            | 0.00783662  |
| LTB         | 207339_s_at  | lymphotoxin beta (TNF superfamily, member 3)                                                                     | 0.008947887 |
| FAM113B     | 228298_at    | family with sequence similarity 113, member B                                                                    | 0.008947887 |
| BRDG1       | 220059_at    |                                                                                                                  | 0.011013653 |
| PRPSAP2     | 203537_at    | phosphoribosyl pyrophosphate synthetase-associated protein 2                                                     | 0.011342898 |
| 244040_at   | 244040_at    |                                                                                                                  | 0.011342898 |
| SEMA4A      | 219259_at    | sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4A | 0.012794771 |
| CD86        | 210895_s_at  | CD86 molecule                                                                                                    | 0.013430782 |
| CD22        | 217422_s_at  | CD22 molecule                                                                                                    | 0.01483858  |
| LIMD1       | 222762_x_at  | LIM domains containing 1                                                                                         | 0.01483858  |
| 236126_at   | 236126_at    |                                                                                                                  | 0.01483858  |
| RUNDC2B     | 1554413_s_at | RUN domain containing 2B                                                                                         | 0.01483858  |
| LOXL2       | 202998_s_at  | lysyl oxidase-like 2                                                                                             | 0.015908888 |
| GOLPH2      | 217771_at    | golgi phosphoprotein 2                                                                                           | 0.015908888 |
| RASGRP3     | 205801_s_at  | RAS guanyl releasing protein 3 (calcium and DAG-regulated)                                                       | 0.015908888 |
| C21orf7     | 221211_s_at  | chromosome 21 open reading frame 7                                                                               | 0.016054465 |
| RAP1A       | 202362_at    | RAP1A, member of RAS oncogene family                                                                             | 0.016642805 |
| ANKRD13A    | 224810_s_at  | ankyrin repeat domain 13A                                                                                        | 0.016798331 |
| ZNF32       | 209538_at    | zinc finger protein 32                                                                                           | 0.017041183 |
| DAAM1       | 216060_s_at  | dishevelled associated activator of morphogenesis 1                                                              | 0.017041183 |
| CRTC3       | 218648_at    | CREB regulated transcription coactivator 3                                                                       | 0.017041183 |
| C13orf31    | 228937_at    | chromosome 13 open reading frame 31                                                                              | 0.017041183 |
| SMAP1L      | 225282_at    | stromal membrane-associated protein 1-like                                                                       | 0.017041183 |
| 224811_at   | 224811_at    |                                                                                                                  | 0.017041183 |
| KCNN3       | 205903_s_at  | potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3                        | 0.017041183 |
| S100Z       | 1554876_a_at | S100 calcium binding protein, zeta                                                                               | 0.017041183 |
| FZD1        | 204451_at    | frizzled homolog 1 (Drosophila)                                                                                  | 0.017041183 |
| FLVCR       | 222906_at    |                                                                                                                  | 0.017041183 |
| MYBL1       | 213906_at    | v-myb myeloblastosis viral oncogene homolog (avian)-like 1                                                       | 0.017041183 |
| EHBP1       | 212653_s_at  | EH domain binding protein 1                                                                                      | 0.017041183 |

| Gene Symbol | Probe       | Description                                                                       | adj.P.Val   |
|-------------|-------------|-----------------------------------------------------------------------------------|-------------|
| SYNE2       | 242774_at   | spectrin repeat containing, nuclear envelope 2                                    | 0.018508325 |
| FLJ36492    | 1557366_at  |                                                                                   | 0.018508325 |
| MAP2K1      | 202670_at   | mitogen-activated protein kinase 1                                                | 0.018508325 |
| NEIL1       | 219396_s_at | nei endonuclease VIII-like 1 (E. coli)                                            | 0.018534278 |
| 228191_at   | 228191_at   |                                                                                   | 0.018813942 |
| LOC389203   | 225014_at   |                                                                                   | 0.02072242  |
| OPN3        | 219032_x_at | opsin 3 (encephalopsin, panopsin)                                                 | 0.021965295 |
| 227539_at   | 227539_at   |                                                                                   | 0.022123902 |
| GCHFR       | 204867_at   | GTP cyclohydrolase I feedback regulator                                           | 0.024418721 |
| 239287_at   | 239287_at   |                                                                                   | 0.024681541 |
| B3GALNT2    | 226233_at   | beta-1,3-N-acetylgalactosaminyltransferase 2                                      | 0.024681541 |
| ANUBL1      | 223624_at   | AN1, ubiquitin-like, homolog (Xenopus laevis)                                     | 0.024681541 |
| 241879_at   | 241879_at   |                                                                                   | 0.026428191 |
| HDAC1       | 201209_at   | histone deacetylase 1                                                             | 0.027641246 |
| FHL1        | 201540_at   | four and a half LIM domains 1                                                     | 0.027802063 |
| PON2        | 201876_at   | paraoxonase 2                                                                     | 0.028969668 |
| DNMT1       | 227684_at   | DNA (cytosine-5-)-methyltransferase 1                                             | 0.030015625 |
| GABARAP L2  | 209046_s_at | GABA(A) receptor-associated protein-like 2                                        | 0.031517586 |
| HSP90B1     | 216449_x_at | heat shock protein 90kDa beta (Grp94), member 1                                   | 0.031894346 |
| RRAS2       | 212590_at   | related RAS viral (r-ras) oncogene homolog 2                                      | 0.032663885 |
| ARSG        | 230748_at   | arylsulfatase G                                                                   | 0.03380232  |
| UGDH        | 203343_at   | UDP-glucose dehydrogenase                                                         | 0.03380232  |
| KCNMB4      | 222857_s_at | potassium large conductance calcium-activated channel, subfamily M, beta member 4 | 0.03380232  |
| SYTL1       | 227134_at   | synaptotagmin-like 1                                                              | 0.034025836 |
| CYFIP1      | 208923_at   | cytoplasmic FMR1 interacting protein 1                                            | 0.035718667 |
| HIPK2       | 225368_at   | homeodomain interacting protein kinase 2                                          | 0.035718667 |
| MAN2A2      | 202032_s_at | mannosidase, alpha, class 2A, member 2                                            | 0.035718667 |
| AAK1        | 225522_at   | AP2 associated kinase 1                                                           | 0.035782217 |
| TBPL1       | 208398_s_at | TBP-like 1                                                                        | 0.036337106 |
| 1553979_at  | 1553979_at  |                                                                                   | 0.037283374 |
| CHML        | 226350_at   | choroideremia-like (Rab escort protein 2)                                         | 0.037979419 |
| VAR5        | 201796_s_at | valyl-tRNA synthetase                                                             | 0.037979419 |
| PTK2        | 208820_at   | PTK2 protein tyrosine kinase 2                                                    | 0.037979419 |
| IGF1R       | 203627_at   | insulin-like growth factor 1 receptor                                             | 0.037979419 |
| GRB2        | 215075_s_at | growth factor receptor-bound protein 2                                            | 0.039960264 |
| ATP8A1      | 213106_at   | ATPase, aminophospholipid transporter (APLT), Class I, type 8A, member 1          | 0.039960264 |
| FZD3        | 219683_at   | frizzled homolog 3 (Drosophila)                                                   | 0.041405941 |
| KIF1B       | 225878_at   | kinesin family member 1B                                                          | 0.041405941 |

| Gene Symbol | Probe        | Description                                                                                    | adj.P.Val   |
|-------------|--------------|------------------------------------------------------------------------------------------------|-------------|
| UBXD2       | 212008_at    | UBX domain containing 2                                                                        | 0.041405941 |
| TMEM87A     | 212202_s_at  | transmembrane protein 87A                                                                      | 0.041888206 |
| PARVB       | 37965_at     | parvin, beta                                                                                   | 0.042377536 |
| SLC26A2     | 205097_at    | solute carrier family 26 (sulfate transporter), member 2                                       | 0.042377536 |
| FCRLM1      | 235400_at    | Fc receptor-like and mucin-like 1                                                              | 0.042377536 |
| PDGFD       | 219304_s_at  | platelet derived growth factor D                                                               | 0.043219716 |
| PRDX4       | 201923_at    | peroxiredoxin 4                                                                                | 0.043219716 |
| SERPINA9    | 1553499_s_at | serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 9            | 0.043248911 |
| C6orf62     | 222309_at    | chromosome 6 open reading frame 62                                                             | 0.043554388 |
| 226525_at   | 226525_at    |                                                                                                | 0.043554388 |
| TOB1        | 228834_at    | transducer of ERBB2, 1                                                                         | 0.043554388 |
| 228242_at   | 228242_at    |                                                                                                | 0.043742426 |
| PKHD1L1     | 230673_at    | polycystic kidney and hepatic disease 1 (autosomal recessive)-like 1                           | 0.04395172  |
| KLHL6       | 1560396_at   | kelch-like 6 (Drosophila)                                                                      | 0.04395172  |
| ASB2        | 227915_at    | ankyrin repeat and SOCS box-containing 2                                                       | 0.044799524 |
| PLEKHF2     | 222699_s_at  | pleckstrin homology domain containing, family F (with FYVE domain) member 2                    | 0.046489788 |
| KLHL23      | 213610_s_at  | kelch-like 23 (Drosophila)                                                                     | 0.046489788 |
| CPNE2       | 225129_at    | copine II                                                                                      | 0.046489788 |
| LOC642236   | 215160_x_at  |                                                                                                | 0.047687714 |
| GALNT2      | 217787_s_at  | UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 2 (GalNAc-T2) | 0.047687714 |
| CD180       | 206206_at    | CD180 molecule                                                                                 | 0.047687714 |
| CPNE5       | 227189_at    | copine V                                                                                       | 0.047687714 |
| FH          | 203032_s_at  | fumarate hydratase                                                                             | 0.047687714 |
| KIF14       | 206364_at    | kinesin family member 14                                                                       | 0.047687714 |
| PEA15       | 200787_s_at  | phosphoprotein enriched in astrocytes 15                                                       | 0.047687714 |
| TOX         | 204529_s_at  |                                                                                                | 0.047687714 |
| MRPS31      | 212604_at    | mitochondrial ribosomal protein S31                                                            | 0.047687714 |
| SEC23A      | 204344_s_at  | Sec23 homolog A (S. cerevisiae)                                                                | 0.047687714 |
| DPYD        | 204646_at    | dihydropyrimidine dehydrogenase                                                                | 0.047864579 |
| 227107_at   | 227107_at    |                                                                                                | 0.047864579 |
| RAB11FIP1   | 219681_s_at  | RAB11 family interacting protein 1 (class I)                                                   | 0.047864579 |
| C1orf107    | 214193_s_at  | chromosome 1 open reading frame 107                                                            | 0.047864579 |
| ATXN10      | 208833_s_at  | ataxin 10                                                                                      | 0.048252462 |
| CPEB4       | 224831_at    | cytoplasmic polyadenylation element binding protein 4                                          | 0.048504075 |

Table 3.

| Symbol    | Probe        | Description                                                                                                      | rho          |
|-----------|--------------|------------------------------------------------------------------------------------------------------------------|--------------|
| SLC30A1   | 228181_at    | solute carrier family 30 (zinc transporter), member 1                                                            | 0.754838311  |
| EPDR1     | 223253_at    | ependymin related protein 1 (zebrafish)                                                                          | 0.733893852  |
| FZD1      | 204451_at    | frizzled homolog 1 (Drosophila)                                                                                  | 0.732218295  |
| MAN2A2    | 202032_s_at  | mannosidase, alpha, class 2A, member 2                                                                           | 0.721327176  |
| PVRIG     | 219812_at    |                                                                                                                  | -0.715881617 |
| EHBP1     | 212653_s_at  | EH domain binding protein 1                                                                                      | 0.706666055  |
| DAAM1     | 226666_at    | G protein-coupled receptor 135                                                                                   | -0.705409387 |
| SMAP1L    | 225282_at    | stromal membrane-associated protein 1-like                                                                       | -0.704990498 |
| PRPSAP2   | 203537_at    | phosphoribosyl pyrophosphate synthetase-associated protein 2                                                     | -0.702896052 |
| HSP90B1   | 216449_x_at  | heat shock protein 90kDa beta (Grp94), member 1                                                                  | 0.691586044  |
| ZNF322A   | 219376_at    | zinc finger protein 322A                                                                                         | 0.690748265  |
| TMEM87A   | 212202_s_at  | transmembrane protein 87A                                                                                        | 0.68823493   |
| RABGAP1L  | 213982_s_at  | RAB GTPase activating protein 1-like                                                                             | -0.681951593 |
| EAF2      | 219551_at    | ELL associated factor 2                                                                                          | -0.681532703 |
| KCNMB4    | 234034_at    | potassium large conductance calcium-activated channel, subfamily M, beta member 4                                | -0.673992698 |
| LCK       | 204891_s_at  | lymphocyte-specific protein tyrosine kinase                                                                      | -0.668547139 |
| RGS13     | 1568752_s_at | regulator of G-protein signalling 13                                                                             | -0.666452693 |
| TOB1      | 228834_at    | transducer of ERBB2, 1                                                                                           | -0.663520468 |
| PLEKHF2   | 218640_s_at  | pleckstrin homology domain containing, family F (with FYVE domain) member 2                                      | -0.66268269  |
| TBPL1     | 208398_s_at  | TBP-like 1                                                                                                       | -0.658912687 |
| KLHL23    | 230434_at    | kelch-like 23 (Drosophila)                                                                                       | 0.658493798  |
| SEMA4C    | 46665_at     | sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4C | 0.658074909  |
| CRTC3     | 218648_at    | CREB regulated transcription coactivator 3                                                                       | 0.657237131  |
| 237075_at | 237075_at    |                                                                                                                  | -0.657237131 |
| GCS1      | 210627_s_at  |                                                                                                                  | 0.650534904  |
| CPNE2     | 225129_at    | copine II                                                                                                        | 0.642576009  |
| PIGL      | 205873_at    | phosphatidylinositol glycan anchor biosynthesis, class L                                                         | -0.64215712  |
| MTHFR     | 239035_at    | 5,10-methylenetetrahydrofolate reductase (NADPH)                                                                 | -0.64215712  |
| ENTPD6    | 201704_at    | ectonucleoside triphosphate diphosphohydrolase 6 (putative function)                                             | 0.641319342  |
| CD22      | 204581_at    | CD22 molecule                                                                                                    | -0.640062674 |
| TPD52     | 201691_s_at  | tumor protein D52                                                                                                | -0.637549339 |

| Symbol    | Probe        | Description                                                                                    | rho          |
|-----------|--------------|------------------------------------------------------------------------------------------------|--------------|
| GPSM1     | 226043_at    | G-protein signalling modulator 1 (AGS3-like, <i>C. elegans</i> )                               | 0.633360447  |
| 239467_at | 239467_at    |                                                                                                | -0.632941558 |
| ROCK1     | 213044_at    | Rho-associated, coiled-coil containing protein kinase 1                                        | -0.632522669 |
| CENTB2    | 212476_at    | centaurin, beta 2                                                                              | -0.630847112 |
| WIPF1     | 231182_at    | Wiskott-Aldrich syndrome protein interacting protein                                           | -0.629590445 |
| RAB11FIP1 | 219681_s at  | RAB11 family interacting protein 1 (class I)                                                   | -0.628333777 |
| LPP       | 202822_at    | LIM domain containing preferred translocation partner in lipoma                                | -0.627077109 |
| FLJ22814  | 220674_at    |                                                                                                | -0.62665822  |
| TRAP1     | 228929_at    | TNF receptor-associated protein 1                                                              | -0.62665822  |
| MRPS31    | 212603_at    | mitochondrial ribosomal protein S31                                                            | -0.625401553 |
| ANKRD13A  | 224810_s at  | ankyrin repeat domain 13A                                                                      | -0.625401553 |
| GALNT2    | 217788_s at  | UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 2 (GalNAc-T2) | 0.624982664  |
| ACVR2B    | 236126_at    |                                                                                                | 0.623160484  |
| CD180     | 206206_at    | CD180 molecule                                                                                 | -0.62163155  |
| IXL       | 225708_at    | intersex-like ( <i>Drosophila</i> )                                                            | 0.62163155   |
| FAM113B   | 228298_at    | family with sequence similarity 113, member B                                                  | -0.621212661 |
| MEF2B     | 205124_at    | MADS box transcription enhancer factor 2, polypeptide B (myocyte enhancer factor 2B)           | -0.620793772 |
| 224811_at | 224811_at    |                                                                                                | -0.620374882 |
| ATP6V1A   | 201972_at    | ATPase, H <sup>+</sup> transporting, lysosomal 70kDa, V1 subunit A                             | -0.619955993 |
| SLC15A2   | 205316_at    | solute carrier family 15 (H <sup>+</sup> /peptide transporter), member 2                       | -0.618280437 |
| RTN4IP1   | 224509_s at  | reticulon 4 interacting protein 1                                                              | -0.618280437 |
| TTC9      | 213174_at    | tetratricopeptide repeat domain 9                                                              | -0.615767101 |
| PTPRC     | 212587_s at  | protein tyrosine phosphatase, receptor type, C                                                 | -0.615348212 |
| FLJ43663  | 228702_at    |                                                                                                | -0.615348212 |
| MARCH6    | 201736_s at  | membrane-associated ring finger (C3HC4) 6                                                      | 0.615348212  |
| C13orf31  | 228937_at    | chromosome 13 open reading frame 31                                                            | -0.614929323 |
| CNOT6L    | 226153_s at  | CCR4-NOT transcription complex, subunit 6-like                                                 | -0.614091545 |
| PIGW      | 1558292_s at | phosphatidylinositol glycan anchor biosynthesis, class W                                       | 0.61115932   |
| ARTS-1    | 210385_s at  |                                                                                                | 0.610740431  |
| RYK       | 216976_s at  | RYK receptor-like tyrosine kinase                                                              | 0.609483764  |
| VNN2      | 205922_at    | vanin 2                                                                                        | -0.609483764 |

| Symbol    | Probe        | Description                                                                         | rho          |
|-----------|--------------|-------------------------------------------------------------------------------------|--------------|
| FNTB      | 204764_at    | farnesyltransferase, CAAX box, beta                                                 | 0.608645985  |
| BICD1     | 242052_at    | bicaudal D homolog 1 (Drosophila)                                                   | -0.607808207 |
| SEPT8     | 209000_s_at  | septin 8                                                                            | 0.606970429  |
| WDR6      | 233573_s_at  | WD repeat domain 6                                                                  | 0.606551539  |
| HDAC1     | 201209_at    | histone deacetylase 1                                                               | -0.604038204 |
| ATP2B4    | 212135_s_at  | ATPase, Ca <sup>++</sup> transporting, plasma membrane 4                            | 0.604038204  |
| BRDG1     | 220059_at    |                                                                                     | -0.602781537 |
| SERPINA9  | 1553499_s_at | serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 9 | -0.602362648 |
| CRSP6     | 221517_s_at  | cofactor required for Sp1 transcriptional activation, subunit 6, 77kDa              | 0.602362648  |
| TMEM17    | 1557137_at   | transmembrane protein 17                                                            | 0.602362648  |
| BPNT1     | 232103_at    | 3'(2'), 5'-bisphosphate nucleotidase 1                                              | -0.601943758 |
| 242826_at | 242826_at    |                                                                                     | -0.601524869 |
| NCOA3     | 207700_s_at  | nuclear receptor coactivator 3                                                      | -0.598592645 |
| LRMP      | 35974_at     | lymphoid-restricted membrane protein                                                | -0.598592645 |
| PTK2      | 208820_at    | PTK2 protein tyrosine kinase 2                                                      | -0.598173756 |
| C21orf7   | 221211_s_at  | chromosome 21 open reading frame 7                                                  | -0.598173756 |
| FCRL3     | 231093_at    | Fc receptor-like 3                                                                  | -0.598173756 |
| FDFT1     | 208647_at    | farnesyl-diphosphate farnesyltransferase 1                                          | -0.597335977 |
| DHX38     | 209178_at    | DEAH (Asp-Glu-Ala-His) box polypeptide 38                                           | 0.596917088  |
| C1orf57   | 223272_s_at  | chromosome 1 open reading frame 57                                                  | 0.596917088  |
| ARSG      | 230748_at    | arylsulfatase G                                                                     | -0.595660421 |
| MS4A7     | 223343_at    | membrane-spanning 4-domains, subfamily A, member 7                                  | -0.595241531 |
| CYP39A1   | 244407_at    | cytochrome P450, family 39, subfamily A, polypeptide 1                              | -0.594403753 |
| DCK       | 203302_at    | deoxycytidine kinase                                                                | -0.593565975 |
| CTNNA1    | 1558214_s_at | catenin (cadherin-associated protein), alpha 1, 102kDa                              | 0.593565975  |
| SLC27A2   | 205769_at    | solute carrier family 27 (fatty acid transporter), member 2                         | 0.592728196  |
| SLC35B2   | 224716_at    | solute carrier family 35, member B2                                                 | 0.592309307  |
| 243185_at | 243185_at    |                                                                                     | -0.592309307 |
| FAM89B    | 32209_at     | family with sequence similarity 89, member B                                        | 0.591890418  |
| GSG2      | 223759_s_at  | germ cell associated 2 (haspin)                                                     | -0.591471529 |
| USP6NL    | 204761_at    | USP6 N-terminal like                                                                | -0.59105264  |
| ATPIF1    | 218671_s_at  | ATPase inhibitory factor 1                                                          | -0.590214861 |
| SLAMF6    | 1552497_a_at | SLAM family member 6                                                                | -0.590214861 |
| TARSL2    | 227611_at    | threonyl-tRNA synthetase-like 2                                                     | 0.590214861  |
| XKR6      | 236047_at    | XK, Kell blood group complex subunit-related family, member 6                       | -0.589377083 |
| 228242_at | 228242_at    |                                                                                     | 0.588958194  |

| Symbol    | Probe        | Description                                                                                 | rho          |
|-----------|--------------|---------------------------------------------------------------------------------------------|--------------|
| EYA3      | 1552314_a_at | eyes absent homolog 3 (Drosophila)                                                          | -0.586863748 |
| RUNDC2B   | 1554413_s_at | RUN domain containing 2B                                                                    | -0.584350413 |
| BXDC5     | 218462_at    | brix domain containing 5                                                                    | -0.583512634 |
| SLC26A2   | 205097_at    | solute carrier family 26 (sulfate transporter), member 2                                    | 0.583512634  |
| PNMA1     | 218224_at    | paraneoplastic antigen MA1                                                                  | 0.583512634  |
| LOC401504 | 226635_at    |                                                                                             | -0.583093745 |
| GPR82     | 1553316_at   | G protein-coupled receptor 82                                                               | -0.582674856 |
| ZBTB9     | 226163_at    | zinc finger and BTB domain containing 9                                                     | 0.582255967  |
| BFSP2     | 207399_at    | beaded filament structural protein 2, phakinin                                              | -0.580999299 |
| SLC6A16   | 219820_at    | solute carrier family 6, member 16                                                          | -0.580999299 |
| SBNO2     | 204166_at    | KIAA0963                                                                                    | 0.580161521  |
| CTSC      | 201487_at    | cathepsin C                                                                                 | 0.579323742  |
| EID1      | 208669_s_at  | CREBBP/EP300 inhibitor 1                                                                    | 0.579323742  |
| RRAS2     | 212589_at    | related RAS viral (r-ras) oncogene homolog 2                                                | -0.578904853 |
| NLK       | 238624_at    | nemo-like kinase                                                                            | -0.578904853 |
| FLJ36492  | 1557366_at   |                                                                                             | -0.578904853 |
| RALGDS    | 209051_s_at  | ral guanine nucleotide dissociation stimulator                                              | 0.578485964  |
| CIRBP     | 225191_at    | cold inducible RNA binding protein                                                          | 0.578067075  |
| P4HB      | 1564494_s_at | procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), beta polypeptide | 0.578067075  |
| ATG3      | 221492_s_at  | ATG3 autophagy related 3 homolog (S. cerevisiae)                                            | -0.578067075 |
| 227539_at | 227539_at    |                                                                                             | -0.577648186 |
| FLJ10815  | 56821_at     |                                                                                             | 0.577648186  |
| C19orf54  | 222052_at    | chromosome 19 open reading frame 54                                                         | -0.577229296 |
| PORCN     | 219483_s_at  | porcupine homolog (Drosophila)                                                              | 0.576810407  |
| PDE6D     | 204091_at    | phosphodiesterase 6D, cGMP-specific, rod, delta                                             | -0.576391518 |
| LOC389203 | 225014_at    |                                                                                             | -0.576391518 |
| 235018_at | 235018_at    |                                                                                             | -0.575134851 |
| CDK10     | 210622_x_at  | cyclin-dependent kinase (CDC2-like) 10                                                      | 0.575134851  |
| KYNU      | 210662_at    | kynureninase (L-kynurenine hydrolase)                                                       | -0.573878183 |
| PIGG      | 218652_s_at  | phosphatidylinositol glycan anchor biosynthesis, class G                                    | 0.573878183  |
| TMEM64    | 225972_at    | transmembrane protein 64                                                                    | -0.573878183 |
| NEDD9     | 240019_at    | neural precursor cell expressed, developmentally down-regulated 9                           | -0.573878183 |

Table 4.

| Symbol | Probes | Description | logFC | Adj.P.value | rho |
|--------|--------|-------------|-------|-------------|-----|
|--------|--------|-------------|-------|-------------|-----|

| Symbol    | Probes                  | Description                                                                                    | logFC       | Adj.P.value | rho   |
|-----------|-------------------------|------------------------------------------------------------------------------------------------|-------------|-------------|-------|
| EPDR1     | 223253_at               | ependymin related protein 1 (zebrafish)                                                        | -6.71079565 | 4.3441E-04  | 0.734 |
| HIPK2     | 225368_at               | NA                                                                                             | 5.568390135 | 3.5719E-02  | NA    |
| CYFIP1    | 208923_at               | NA                                                                                             | 5.507430049 | 3.5719E-02  | NA    |
| GOLPH2    | 217771_at               | NA                                                                                             | 5.149533123 | 1.5909E-02  | NA    |
| PON2      | 201876_at               | NA                                                                                             | -5.02937768 | 2.8970E-02  | NA    |
| OPN3      | 219032_x_at             | NA                                                                                             | 4.868576042 | 2.1965E-02  | NA    |
| FHL1      | 201540_at               | NA                                                                                             | 4.849936383 | 2.7802E-02  | NA    |
| DPYD      | 204646_at               | NA                                                                                             | 4.601899147 | 4.7865E-02  | NA    |
| CRTC3     | 218648_at               | CREB regulated transcription coactivator 3                                                     | 4.447380308 | 1.7041E-02  | 0.657 |
| LIMD1     | 222762_x_at             | NA                                                                                             | 4.385468009 | 1.4839E-02  | NA    |
| IGF1R     | 203627_at               | NA                                                                                             | 3.780119703 | 3.7979E-02  | NA    |
| PARVB     | 37965_at                | NA                                                                                             | 3.705700946 | 4.2378E-02  | NA    |
| 236126_at | 236126_at               | NA                                                                                             | 3.694482091 | 1.4839E-02  | NA    |
| CHML      | 226350_at               | NA                                                                                             | 3.643899135 | 3.7979E-02  | NA    |
| FZD1      | 204451_at               | frizzled homolog 1 (Drosophila)                                                                | 3.531407505 | 1.7041E-02  | 0.732 |
| AAK1      | 225522_at               | NA                                                                                             | 3.502784982 | 3.5782E-02  | NA    |
| CPNE2     | 225129_at               | copine II                                                                                      | 3.432724459 | 4.6490E-02  | 0.643 |
| KLHL23    | 213610_s_at, 30434_at   | kelch-like 23 (Drosophila)                                                                     | 3.407601857 | 4.6490E-02  | 0.658 |
| ZNF32     | 209538_at               | NA                                                                                             | -3.37444837 | 1.7041E-02  | NA    |
| GALNT2    | 217787_s_at, 17788_s_at | UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 2 (GalNAc-T2) | 3.068993195 | 4.7688E-02  | 0.625 |
| SLC30A1   | 212907_at, 228181_at    | solute carrier family 30 (zinc transporter), member 1                                          | 2.897034114 | 7.8366E-03  | 0.755 |
| KIF1B     | 225878_at               | NA                                                                                             | 2.893360476 | 4.1406E-02  | NA    |
| FZD3      | 219683_at               | NA                                                                                             | 2.888266087 | 4.1406E-02  | NA    |
| SLC26A2   | 205097_at               | solute carrier family 26 (sulfate transporter), member 2                                       | 2.592191782 | 4.2378E-02  | 0.584 |
| VARS      | 201796_s_at             | NA                                                                                             | 2.146698292 | 3.7979E-02  | NA    |

| Symbol     | Probes              | Description                                     | logFC       | Adj.P.value | rho    |
|------------|---------------------|-------------------------------------------------|-------------|-------------|--------|
| MAN2A2     | 202032 s at         | mannosidase, alpha, class 2A, member 2          | -2.05163539 | 3.5719E-02  | 0.721  |
| C6orf62    | 222309 at           | NA                                              | 1.970715812 | 4.3554E-02  | NA     |
| UGDH       | 203343 at           | NA                                              | 1.915040205 | 3.3802E-02  | NA     |
| HSP90B1    | 216449 x at         | heat shock protein 90kDa beta (Grp94), member 1 | 1.779135947 | 3.1894E-02  | 0.692  |
| B3GALNT2   | 226233 at           | NA                                              | 1.591532059 | 2.4682E-02  | NA     |
| FLVCR      | 222906 at           | NA                                              | 1.528203803 | 1.7041E-02  | NA     |
| 227107 at  | 227107 at           | NA                                              | 1.436834856 | 4.7865E-02  | NA     |
| SEC23A     | 204344 s at         | NA                                              | 1.377564142 | 4.7688E-02  | NA     |
| 228242 at  | 228242 at           | NA                                              | 1.314847732 | 4.3742E-02  | 0.589  |
| TMEM87A    | 212202 s at         | transmembrane protein 87A                       | 1.267840163 | 4.1888E-02  | 0.688  |
| 228191 at  | 228191 at           | NA                                              | 1.196685963 | 1.8814E-02  | NA     |
| KIF14      | 206364 at           | NA                                              | 1.150921894 | 4.7688E-02  | NA     |
| EHBP1      | 212653 s at         | EH domain binding protein 1                     | 1.110923792 | 1.7041E-02  | 0.707  |
| C1orf107   | 214193 s at         | NA                                              | 1.102968299 | 4.7865E-02  | NA     |
| UBXD2      | 212008 at           | NA                                              | 1.062833934 | 4.1406E-02  | NA     |
| FH         | 203032 s at         | NA                                              | 1.047497846 | 4.7688E-02  | NA     |
| PRDX4      | 201923 at           | NA                                              | 0.976330782 | 4.3220E-02  | NA     |
| 1553979 at | 1553979 at          | NA                                              | -0.95937263 | 3.7283E-02  | NA     |
| ATXN10     | 208833 s at         | NA                                              | 0.717153159 | 4.8252E-02  | NA     |
| GABARAP L2 | 209046 s at         | NA                                              | 0.928831609 | 3.1518E-02  | NA     |
| MAP2K1     | 202670 at           | NA                                              | 1.062284638 | 1.8508E-02  | NA     |
| LOC642236  | 215160 x at         | NA                                              | 1.091751999 | 4.7688E-02  | NA     |
| MRPS31     | 212604_at,212603_at | mitochondrial ribosomal protein S31             | 1.140136013 | 4.7688E-02  | -0.625 |
| HDAC1      | 201209 at           | histone deacetylase 1                           | 1.189759283 | 2.7641E-02  | -0.604 |
| RAP1A      | 202362 at           | NA                                              | 1.235628621 | 1.6643E-02  | NA     |
| 226525 at  | 226525 at           | NA                                              | 1.46297442  | 4.3554E-02  | NA     |
| TBPL1      | 208398 s at         | TBP-like 1                                      | 1.50757518  | 3.6337E-02  | -0.659 |
| TOB1       | 228834 at           | transducer of ERBB2, 1                          | 1.580519874 | 4.3554E-02  | -0.664 |
| SMAP1L     | 225282 at           | stromal membrane-associated protein 1-like      | 1.582665273 | 1.7041E-02  | -0.705 |
| PEA15      | 200787 s at         | NA                                              | 1.636511829 | 4.7688E-02  | NA     |

| Symbol    | Probes                   | Description                                                                         | logFC       | Adj.P.value | rho    |
|-----------|--------------------------|-------------------------------------------------------------------------------------|-------------|-------------|--------|
| LOC389203 | 225014_at                | NA                                                                                  | 1.653219861 | 2.0722E-02  | -0.576 |
| 227539_at | 227539_at                | NA                                                                                  | 1.706768556 | 2.2124E-02  | -0.578 |
| GRB2      | 215075_s_at              | NA                                                                                  | 1.719009368 | 3.9960E-02  | NA     |
| PRPSAP2   | 203537_at                | phosphoribosyl pyrophosphate synthetase-associated protein 2                        | 1.937200364 | 1.1343E-02  | -0.703 |
| ANKRD13A  | 224810_s_at              | ankyrin repeat domain 13A                                                           | 2.096260555 | 1.6798E-02  | -0.625 |
| DAAM1     | 216060_s_at, 26666_at    | G protein-coupled receptor 135                                                      | 2.205266761 | 1.7041E-02  | -0.705 |
| SYNE2     | 242774_at                | NA                                                                                  | 2.326279517 | 1.8508E-02  | NA     |
| ATP8A1    | 213106_at                | NA                                                                                  | 2.351268406 | 3.9960E-02  | NA     |
| PLEKHF2   | 222699_s_at, 218640_s_at | pleckstrin homology domain containing, family F (with FYVE domain) member 2         | 3.004500438 | 4.6490E-02  | -0.663 |
| S100Z     | 1554876_a_at             | NA                                                                                  | 3.144995156 | 1.7041E-02  | NA     |
| FLJ36492  | 1557366_at               | NA                                                                                  | 3.222537979 | 1.8508E-02  | -0.579 |
| SLAMF6    | 1552497_a_at             | SLAM family member 6                                                                | 3.363017096 | 2.6351E-03  | -0.590 |
| CPEB4     | 224831_at                | NA                                                                                  | 3.444268629 | 4.8504E-02  | NA     |
| NEIL1     | 219396_s_at              | NA                                                                                  | 3.470614786 | 1.8534E-02  | NA     |
| KLHL6     | 1560396_at               | NA                                                                                  | 3.592234269 | 4.3952E-02  | NA     |
| ANUBL1    | 223624_at                | NA                                                                                  | 3.597608491 | 2.4682E-02  | NA     |
| SYTL1     | 227134_at                | NA                                                                                  | 3.601625514 | 3.4026E-02  | NA     |
| LPP       | 202822_at                | LIM domain containing preferred translocation partner in lipoma                     | 3.65635503  | 5.6681E-03  | -0.627 |
| ARSG      | 230748_at                | arylsulfatase G                                                                     | 3.772680821 | 3.3802E-02  | -0.596 |
| DNMT1     | 227684_at                | NA                                                                                  | 3.787896364 | 3.0016E-02  | NA     |
| RAB11FIP1 | 219681_s_at              | RAB11 family interacting protein 1 (class I)                                        | 3.877841023 | 4.7865E-02  | -0.628 |
| 224811_at | 224811_at                | NA                                                                                  | 3.884011816 | 1.7041E-02  | -0.620 |
| 241879_at | 241879_at                | NA                                                                                  | 3.897073844 | 2.6428E-02  | NA     |
| MYBL1     | 213906_at                | NA                                                                                  | 3.964686033 | 1.7041E-02  | NA     |
| KCNN3     | 244040_at                | potassium large conductance calcium-activated channel, subfamily M, beta member 3   | 4.14713855  | 1.1343E-02  | NA     |
| RUNDC2B   | 1554413_s_at             | RUN domain containing 2B                                                            | 4.249552511 | 1.4839E-02  | -0.584 |
| GCHFR     | 204867_at                | NA                                                                                  | 4.314659424 | 2.4419E-02  | NA     |
| C13orf31  | 228937_at                | chromosome 13 open reading frame 31                                                 | 4.342634637 | 1.7041E-02  | -0.615 |
| KCNN3     | 205903_s_at              | NA                                                                                  | 4.348558398 | 1.7041E-02  | NA     |
| SERPINA9  | 1553499_s_at             | serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 9 | 4.362716185 | 4.3249E-02  | -0.602 |

| Symbol    | Probes                 | Description                                                                          | logFC       | Adj.P.value | rho    |
|-----------|------------------------|--------------------------------------------------------------------------------------|-------------|-------------|--------|
| ASB2      | 227915_at              | NA                                                                                   | 4.393168852 | 4.4800E-02  | NA     |
| CD180     | 206206_at              | CD180 molecule                                                                       | 4.400474176 | 4.7688E-02  | -0.622 |
| SEMA4A    | 219259_at              | NA                                                                                   | 4.461977712 | 1.2795E-02  | NA     |
| PKHD1L1   | 230673_at              | NA                                                                                   | 4.462674523 | 4.3952E-02  | NA     |
| FAM113B   | 228298_at              | family with sequence similarity 113, member B                                        | 4.725746806 | 8.9479E-03  | -0.621 |
| MGC2463   | 219812_at              | NA                                                                                   | 4.747120819 | 1.5799E-04  | NA     |
| PTK2      | 208820_at              | PTK2 protein tyrosine kinase 2                                                       | 4.830737904 | 3.7979E-02  | -0.598 |
| LTB       | 207339_s_at            | NA                                                                                   | 4.861032521 | 8.9479E-03  | NA     |
| LOXL2     | 202998_s_at            | NA                                                                                   | 4.936851624 | 1.5909E-02  | NA     |
| KCNMB4    | 222857_s_at,234034_at  | potassium large conductance calcium-activated channel, subfamily M, beta member 4    | 5.103201059 | 3.3802E-02  | -0.674 |
| PDGFD     | 219304_s_at            | NA                                                                                   | 5.13661915  | 4.3220E-02  | NA     |
| CD22      | 217422_s_at,204581_at  | CD22 molecule                                                                        | 5.283886004 | 1.4839E-02  | -0.640 |
| CPNE5     | 227189_at              | NA                                                                                   | 5.346723772 | 4.7688E-02  | NA     |
| C21orf7   | 221211_s_at            | chromosome 21 open reading frame 7                                                   | 5.407994478 | 1.6054E-02  | -0.598 |
| CD86      | 210895_s_at            | NA                                                                                   | 5.574519784 | 1.3431E-02  | NA     |
| VNN2      | 205922_at              | vanin 2                                                                              | 5.634272247 | 2.4799E-04  | -0.609 |
| TOX       | 204529_s_at            | NA                                                                                   | 5.647082288 | 4.7688E-02  | NA     |
| RASGRP3   | 205801_s_at            | NA                                                                                   | 5.676809838 | 1.5909E-02  | NA     |
| RRAS2     | 212590_at,212589_at    | related RAS viral (r-ras) oncogene homolog 2                                         | 5.694136051 | 3.2664E-02  | -0.579 |
| 239287_at | 239287_at              | NA                                                                                   | 5.91276116  | 2.4682E-02  | NA     |
| MEF2B     | 205124_at              | MADS box transcription enhancer factor 2, polypeptide B (myocyte enhancer factor 2B) | 6.009095593 | 1.3526E-03  | -0.621 |
| BRDG1     | 220059_at              | NA                                                                                   | 6.358345958 | 1.1014E-02  | -0.603 |
| FCRLM1    | 235400_at              | NA                                                                                   | 6.390558096 | 4.2378E-02  | NA     |
| LCK       | 204891_s_at            | lymphocyte-specific protein tyrosine kinase                                          | 7.315280882 | 2.6351E-03  | -0.669 |
| RGS13     | 210258_at,1568752_s_at | regulator of G-protein signalling 13                                                 | 10.29738517 | 2.5700E-05  | -0.666 |
| PVRIG     | 219812_at              | NA                                                                                   | NA          | NA          | -0.716 |
| RABGAP1L  | 213982_s_at            | RAB GTPase activating protein 1-like                                                 | NA          | NA          | -0.682 |
| EAF2      | 219551_at              | ELL associated factor 2                                                              | NA          | NA          | -0.682 |
| 237075_at | 237075_at              | NA                                                                                   | NA          | NA          | -0.657 |

| Symbol    | Probes      | Description                                                              | logFC | Adj.P.value | rho    |
|-----------|-------------|--------------------------------------------------------------------------|-------|-------------|--------|
| MTHFR     | 239035_at   | 5,10-methylenetetrahydrofolate reductase (NADPH)                         | NA    | NA          | -0.642 |
| PIGL      | 205873_at   | phosphatidylinositol glycan anchor biosynthesis, class L                 | NA    | NA          | -0.642 |
| TPD52     | 201691_s_at | tumor protein D52                                                        | NA    | NA          | -0.638 |
| 239467_at | 239467_at   | NA                                                                       | NA    | NA          | -0.633 |
| ROCK1     | 213044_at   | Rho-associated, coiled-coil containing protein kinase 1                  | NA    | NA          | -0.633 |
| CENTB2    | 212476_at   | centaurin, beta 2                                                        | NA    | NA          | -0.631 |
| WIPF1     | 231182_at   | Wiskott-Aldrich syndrome protein interacting protein                     | NA    | NA          | -0.630 |
| FLJ22814  | 220674_at   | NA                                                                       | NA    | NA          | -0.627 |
| TRAP1     | 228929_at   | TNF receptor-associated protein 1                                        | NA    | NA          | -0.627 |
| ATP6V1A   | 201972_at   | ATPase, H <sup>+</sup> transporting, lysosomal 70kDa, V1 subunit A       | NA    | NA          | -0.620 |
| RTN4IP1   | 224509_s_at | reticulon 4 interacting protein 1                                        | NA    | NA          | -0.618 |
| SLC15A2   | 205316_at   | solute carrier family 15 (H <sup>+</sup> /peptide transporter), member 2 | NA    | NA          | -0.618 |
| TTC9      | 213174_at   | tetratricopeptide repeat domain 9                                        | NA    | NA          | -0.616 |
| FLJ43663  | 228702_at   | NA                                                                       | NA    | NA          | -0.615 |
| PTPRC     | 212587_s_at | protein tyrosine phosphatase, receptor type, C                           | NA    | NA          | -0.615 |
| CNOT6L    | 226153_s_at | CCR4-NOT transcription complex, subunit 6-like                           | NA    | NA          | -0.614 |
| BICD1     | 242052_at   | bicaudal D homolog 1 (Drosophila)                                        | NA    | NA          | -0.608 |
| BPNT1     | 232103_at   | 3'(2'), 5'-bisphosphate nucleotidase 1                                   | NA    | NA          | -0.602 |
| KAR       | 242826_at   | 3-ketoacyl-CoA reductase                                                 | NA    | NA          | -0.602 |
| LRMP      | 35974_at    | lymphoid-restricted membrane protein                                     | NA    | NA          | -0.599 |
| NCOA3     | 207700_s_at | nuclear receptor coactivator 3                                           | NA    | NA          | -0.599 |
| FCRL3     | 231093_at   | Fc receptor-like 3                                                       | NA    | NA          | -0.598 |

| Symbol        | Probes       | Description                                                             | logFC | Adj.P.value | rho    |
|---------------|--------------|-------------------------------------------------------------------------|-------|-------------|--------|
| FDFT1         | 208647_at    | farnesyl-diphosphate<br>farnesyltransferase 1                           | NA    | NA          | -0.597 |
| MS4A7         | 223343_at    | membrane-spanning 4-<br>domains, subfamily A,<br>member 7               | NA    | NA          | -0.595 |
| CYP39A1       | 244407_at    | cytochrome P450, family 39,<br>subfamily A, polypeptide 1               | NA    | NA          | -0.594 |
| DCK           | 203302_at    | deoxycytidine kinase                                                    | NA    | NA          | -0.594 |
| 243185_at     | 243185_at    | NA                                                                      | NA    | NA          | -0.592 |
| GSG2          | 223759_s_at  | germ cell associated 2<br>(haspin)                                      | NA    | NA          | -0.591 |
| USP6NL        | 204761_at    | USP6 N-terminal like                                                    | NA    | NA          | -0.591 |
| ATPIF1        | 218671_s_at  | ATPase inhibitory factor 1                                              | NA    | NA          | -0.590 |
| XKR6          | 236047_at    | XK, Kell blood group<br>complex subunit-related<br>family, member 6     | NA    | NA          | -0.589 |
| EYA3          | 1552314_a_at | eyes absent homolog 3<br>(Drosophila)                                   | NA    | NA          | -0.587 |
| BXDC5         | 218462_at    | brix domain containing 5                                                | NA    | NA          | -0.584 |
| LOC40150<br>4 | 226635_at    | NA                                                                      | NA    | NA          | -0.583 |
| GPR82         | 1553316_at   | G protein-coupled receptor<br>82                                        | NA    | NA          | -0.583 |
| BFSP2         | 207399_at    | beaded filament structural<br>protein 2, phakinin                       | NA    | NA          | -0.581 |
| SLC6A16       | 219820_at    | solute carrier family 6,<br>member 16                                   | NA    | NA          | -0.581 |
| NLK           | 238624_at    | nemo-like kinase                                                        | NA    | NA          | -0.579 |
| ATG3          | 221492_s_at  | ATG3 autophagy related 3<br>homolog (S. cerevisiae)                     | NA    | NA          | -0.578 |
| C19orf54      | 222052_at    | chromosome 19 open<br>reading frame 54                                  | NA    | NA          | -0.577 |
| PDE6D         | 204091_at    | phosphodiesterase 6D,<br>cGMP-specific, rod, delta                      | NA    | NA          | -0.576 |
| 235018_at     | 235018_at    | NA                                                                      | NA    | NA          | -0.575 |
| KYNU          | 210662_at    | kynureninase (L-kynurenine<br>hydrolase)                                | NA    | NA          | -0.574 |
| NEDD9         | 240019_at    | neural precursor cell<br>expressed, developmentally<br>down-regulated 9 | NA    | NA          | -0.574 |
| TMEM64        | 225972_at    | transmembrane protein 64                                                | NA    | NA          | -0.574 |
| PIGG          | 218652_s_at  | phosphatidylinositol glycan<br>anchor biosynthesis, class G             | NA    | NA          | 0.574  |

| Symbol   | Probes       | Description                                                                                 | logFC | Adj.P.value | rho   |
|----------|--------------|---------------------------------------------------------------------------------------------|-------|-------------|-------|
| CDK10    | 210622_x_at  | cyclin-dependent kinase (CDC2-like) 10                                                      | NA    | NA          | 0.575 |
| PORCN    | 219483_s_at  | porcupine homolog (Drosophila)                                                              | NA    | NA          | 0.577 |
| FLJ10815 | 56821_at     | NA                                                                                          | NA    | NA          | 0.578 |
| CIRBP    | 225191_at    | cold inducible RNA binding protein                                                          | NA    | NA          | 0.578 |
| P4HB     | 1564494_s_at | procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), beta polypeptide | NA    | NA          | 0.578 |
| RALGDS   | 209051_s_at  | ral guanine nucleotide dissociation stimulator                                              | NA    | NA          | 0.578 |
| CTSC     | 201487_at    | cathepsin C                                                                                 | NA    | NA          | 0.579 |
| EID1     | 208669_s_at  | CREBBP/EP300 inhibitor 1                                                                    | NA    | NA          | 0.579 |
| SBNO2    | 204166_at    | KIAA0963                                                                                    | NA    | NA          | 0.580 |
| ZBTB9    | 226163_at    | zinc finger and BTB domain containing 9                                                     | NA    | NA          | 0.582 |
| PNMA1    | 218224_at    | paraneoplastic antigen MA1                                                                  | NA    | NA          | 0.584 |
| TARSL2   | 227611_at    | threonyl-tRNA synthetase-like 2                                                             | NA    | NA          | 0.590 |
| FAM89B   | 32209_at     | family with sequence similarity 89, member B                                                | NA    | NA          | 0.592 |
| SLC35B2  | 224716_at    | solute carrier family 35, member B2                                                         | NA    | NA          | 0.592 |
| SLC27A2  | 205769_at    | solute carrier family 27 (fatty acid transporter), member 2                                 | NA    | NA          | 0.593 |
| CTNNA1   | 1558214_s_at | catenin (cadherin-associated protein), alpha 1, 102kDa                                      | NA    | NA          | 0.594 |
| C1orf57  | 223272_s_at  | chromosome 1 open reading frame 57                                                          | NA    | NA          | 0.597 |
| DHX38    | 209178_at    | DEAH (Asp-Glu-Ala-His) box polypeptide 38                                                   | NA    | NA          | 0.597 |
| CRSP6    | 221517_s_at  | cofactor required for Sp1 transcriptional activation, subunit 6, 77kDa                      | NA    | NA          | 0.602 |
| TMEM17   | 1557137_at   | transmembrane protein 17                                                                    | NA    | NA          | 0.602 |
| ATP2B4   | 212135_s_at  | ATPase, Ca <sup>++</sup> transporting, plasma membrane 4                                    | NA    | NA          | 0.604 |
| WDR6     | 233573_s_at  | WD repeat domain 6                                                                          | NA    | NA          | 0.607 |

| Symbol  | Probes       | Description                                                                                                      | logFC | Adj.P.value | rho   |
|---------|--------------|------------------------------------------------------------------------------------------------------------------|-------|-------------|-------|
| SEPT8   | 209000_s_at  | septin 8                                                                                                         | NA    | NA          | 0.607 |
| FNTB    | 204764_at    | farnesyltransferase, CAAX box, beta                                                                              | NA    | NA          | 0.609 |
| RYK     | 216976_s_at  | RYK receptor-like tyrosine kinase                                                                                | NA    | NA          | 0.609 |
| ARTS-1  | 210385_s_at  | NA                                                                                                               | NA    | NA          | 0.611 |
| PIGW    | 1558292_s_at | phosphatidylinositol glycan anchor biosynthesis, class W                                                         | NA    | NA          | 0.611 |
| MARCH6  | 201736_s_at  | membrane-associated ring finger (C3HC4) 6                                                                        | NA    | NA          | 0.615 |
| IXL     | 225708_at    | intersex-like (Drosophila)                                                                                       | NA    | NA          | 0.622 |
| ACVR2B  | 236126_at    | NA                                                                                                               | NA    | NA          | 0.623 |
| GPSM1   | 226043_at    | G-protein signalling modulator 1 (AGS3-like, C. elegans)                                                         | NA    | NA          | 0.633 |
| ENTPD6  | 201704_at    | ectonucleoside triphosphate diphosphohydrolase 6 (putative function)                                             | NA    | NA          | 0.641 |
| GCS1    | 210627_s_at  | NA                                                                                                               | NA    | NA          | 0.651 |
| SEMA4C  | 46665_at     | sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4C | NA    | NA          | 0.658 |
| ZNF322A | 219376_at    | zinc finger protein 322A                                                                                         | NA    | NA          | 0.691 |

**[0162]** The genes that are highly expressed in Table 4 may be co-regulated genes that may not be related to the biology of anti-CD40 activity. Therefore to comprehend the biological function of the genes that are differentially expressed between sensitive and resistant cells, we carried out Gene Set Enrichment Analysis (GSEA). In this analysis, we address the question by calculating the mean t-statistic for genes in the set, and then comparing that mean t-statistic to the mean statistics calculated for random sets of genes of the same size. A low p-value may indicate that there is some correlation between the set of genes and the sample classification used to generate the statistics. Gene Set Analysis can thus be interpreted as a summary of the properties of the genes that are highly differentially expressed. Table 5 provides gene set enrichment analysis of anti-CD40 Ab.1 Sensitive vs. Resistant NHL cell lines. Enriched gene sets, number of genes per gene set, normalized enrichment score (NES), and nominal p-value (NOM p-val) are displayed. The higher the NES and the lower the NOM p-val, the more likely the findings are significant.

Table 5.

| Gene Set Name                 | Number of Genes | NES       | NOM p-val   |
|-------------------------------|-----------------|-----------|-------------|
| BCRPATHWAY                    | 35              | 1.5387669 | 0.018181818 |
| BASSO_GERMINAL_CENTER-CD40_DN | 70              | 1.5124674 | 0.016949153 |

[0163] Of the GSEA identified gene sets that were biologically relevant, gene sets involved in B-cell Receptor Signaling (BCR) and genes that are of germinal center origin (Table 5) were enriched. Of primary interest is the observation of genes involved in CD40 signaling as determined by the BASSO\_GERMINAL\_CENTER\_CD40\_DN gene set (Figure 1). Basso et al., Blood 104:4088-96, 2004. This gene set refers to genes that have been reported to be repressed by CD40L in a Ramos cell line. The rank and adjusted p-value from the differentially expressed gene list is displayed in Table 6 with respect to this gene set. In Table 6, differentially expressed genes between sensitive and resistant cell lines are enriched for genes that are known to be CD40L downregulated. Ranked genes are derived from the moderated t-test (Table 2). 70 genes in total were part of this gene set with the top 11 being displayed in this table. Genes shown in table 6 were overexpressed in anti-CD40 Ab.1 sensitive cell lines. The partial overlap of genes with the BCR and CD40L genes is expected since the two signal transduction pathways converge at the axis of NF- $\kappa$ B transcription and both pathways can synergize to activate B-cells. We next ascertained if any of the CD40L-induced genes are capable of discriminating between sensitive and resistant NHL cell lines to anti-CD40 Ab.1. Of the CD40L genes within the differentially expressed gene list on Tables 2 and 3, VNN2 gave the most accurate discrimination for sensitive and resistant cell lines (Figure 2).

Table 6.

| Rank | Gene Symbol | ProbeID     | Description                                                                          | t-statistic | pvalue   | adj.P.Val. |
|------|-------------|-------------|--------------------------------------------------------------------------------------|-------------|----------|------------|
| 3    | VNN2        | 205922_at   | vanin 2                                                                              | 7.2679      | 0        | 0.000248   |
| 5    | MEF2C       | 205124_at   | MADS box transcription enhancer factor 2, polypeptide B (myocyte enhancer factor 2B) | 6.7125      | 0        | 0.001353   |
| 10   | LTB         | 207339_s_at | lymphotoxin beta (TNF superfamily, member 3)                                         | 4.8723      | 1.00E-04 | 0.008948   |

| Rank | Gene Symbol | ProbeID     | Description                                                                               | t-statistic | pvalue   | adj.P.Val. |
|------|-------------|-------------|-------------------------------------------------------------------------------------------|-------------|----------|------------|
| 14   | KCNN3       | 244040_at   | potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3 | 5.4914      | 0        | 0.011343   |
| 252  | NCF1        | 204961_s_at | NCF1                                                                                      | 4.0453      | 6.00E-04 | 0.094030   |
| 278  | BCL6        | 203140_at   | B-cell CLL/lymphoma 6 (zinc finger protein 51)                                            | 4.3355      | 3.00E-04 | 0.098016   |
| 349  | IGJ         | 212592_at   | immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides | 3.6952      | 0.0013   | 0.109865   |
| 475  | ELTI1902    | 207761_s_at | methyltransferase like 7A                                                                 | 3.3433      | 0.0031   | 0.130104   |
| 498  | PNOC        | 205901_at   | prepronociceptin                                                                          | 3.7812      | 0.0011   | 0.134773   |
| 548  | CSF2RB      | 205159_at   | colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)         | 3.3371      | 0.0031   | 0.146260   |
| 707  | POU2AF1     | 205267_at   | POU domain, class 2, associating factor 1                                                 | 3.3788      | 0.0028   | 0.171312   |

[0164] Further inspection of the differentially expressed genes list also revealed genes such as CD22, RGS13, and MEF2B (Table 2 and Figures 3, 4, 6), that were indicative of germinal center B (GCB) cells were overexpressed in anti-CD40 Ab.1 sensitive cell lines. CD40 signature genes correlated with anti-CD40.Ab.1 sensitivity as shown in Figure 5. Notably, RGS13 was one of the highest-ranking genes by moderated t-test (Table 2) and Spearman's rank correlation (Table 3) across the cell lines and as a single gene can discriminate between sensitive and resistant as well intermediate and resistant classes with high accuracy: 96% accuracy for sensitive vs. resistant. 81% for intermediate vs. resistant, and 87% for sensitive/intermediate vs. resistant.

[0165] To gain optimal classification accuracy it will likely require a gene signature, or metagene, classifier. Therefore, to identify genes that may contribute to the most accurate classifier we generated an algorithm to identify pairs of genes that when combined would give the best possible classification across the cell lines with respect to anti-CD40 Ab.1 sensitivity. We therefore carried out a Stepwise Linear Modeling to achieve this aim and the final gene selection is shown in Table 7. In Table 7, each target gene is shown with its corresponding inversely correlated (anti-correlated) Pair Gene, in order of the step at which the Target Gene was chosen for inclusion in the Index, as described earlier. This selection of gene pairs revealed a robust classification of Sensitive, Intermediate and Resistant classes to

anti-CD40 Ab.1 (Figure 4) when a Sensitivity Index was calculated, which is essentially the sum of signed t-scores for log2-scale expression of Gene Pairs 1-8.

Table 7. Anti-CD40 Ab.1 Sensitivity Index Identified Using Stepwise Linear Modeling.

| Gene Pair # | Step # | Main Gene Symbol | Main Gene Probe | Fold Change Estimate | Pair Gene Symbol | Pair Gene Probe | Correlation with Main Gene |
|-------------|--------|------------------|-----------------|----------------------|------------------|-----------------|----------------------------|
| 1           | 1      | VNN2             | 205922_at       | +2.63                | EPDR1            | 223253_at       | -0.72                      |
| 2           | 1      | RGS13            | 210258_at       | +5.18                | EPDR1            | 223253_at       | -0.88                      |
| 3           | 1      | CD22             | 204581_at       | +2.70                | EPDR1            | 223253_at       | -0.68                      |
| 4           | 2      | LRRC8A           | 233487_s_at     | -0.50                | PRPSAP2          | 203537_at       | -0.61                      |
| 5           | 3      | CD40             | 205153_s_at     | +1.47                | IGF1R            | 203627_at       | -0.76                      |
| 6           | 4      | IFITM1           | 214022_s_at     | -2.01                | BTG2             | 201236_s_at     | -0.56                      |
| 7           | 5      | SMN1             | 203852_s_at     | +0.36                | LMO2             | 204249_s_at     | -0.49                      |
| 8           | 6      | PRKCA            | 213093_at       | -1.34                | YIPF3            | 216338_s_at     | -0.72                      |
| 9           | 7      | BCL6             | 203140_at       | NA                   | NA               | NA              | NA                         |

**[0166]** Overall, CD40L plays a critical role in activating B-cells and results in the expansion and proliferation of B-cells as well as Ig class switching and the CD40L signaling pathway is also active within pre- and post-GCB-cells including naïve and memory B-cells. Therefore, it is striking to note that NHL cells that are displaying sensitivity to anti-CD40 Ab.1 are similar to GCB-cells in origin by gene expression profiling and have CD40L downregulated genes highly expressed, in contrast to resistant cells, indicative of a relationship between GCB and CD40 pathway activation status determining sensitivity to anti-CD40 Ab.1.

**[0167]** To further confirm predictive classifier, xenograft models are used to explore in therapy (such as combination therapy). Real time quantitative RT-PCR (qRT-PCR) is used for measuring gene expression levels. After confirming the predictive classifier, immunohistochemistry (IHC) assays are developed for a small group of markers selected (*e.g.*, VNN2 and RGS13). Selected marker genes are further tested in clinical trial samples.

**[0168]** qRT-PCR and IHC are performed to measure expression levels of selected marker genes in clinical trial samples. Expression levels in samples from patients having relapsed

diffuse large B-cell lymphoma that are responsive to the anti-CD40 treatment are compared the expression levels in samples from patients that are not responsive to the treatment.

**Example 2. Identification of markers associated with responsiveness to treatment with anti-CD40 Ab.1 in clinical trials**

*Clinical Trial 001 (Phase II)*

[0169] 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.

*Clinical Trial 002 (Phase I)*

[0170] 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*

**[0171]** 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).

**[0172]** 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 10.

Table 10. Primers and Probes

| Gene Locus  | GenBank Accession No. | Probe Overlap | Forward Primer                                | Reverse Primer                                      | Probe                                     |
|-------------|-----------------------|---------------|-----------------------------------------------|-----------------------------------------------------|-------------------------------------------|
| PRKCA       | NM_002737.2           | 1             | TGACAAAATGTAGAGGCCATTCA<br>(SEQ ID NO:3)      | CATCCGTCCTCTTGGCATATAA<br>(SEQ ID NO:4)             | CCGTAAACACCATTT<br>(SEQ ID NO:5)          |
| IGF1R       | NM_000875.3           | 1             | TTGCAAGGAAAGAAATTCAAACAC<br>(SEQ ID NO:6)     | TGCTTGAATCCATGACTGCTT<br>(SEQ ID NO:7)              | ACAACAGCAGTAAGAAGA<br>(SEQ ID NO:8)       |
| BTG2        | NM_006763.2           | 1             | CAGGTCCCTGCCTTTTATAGAAG<br>(SEQ ID NO:9)      | ATCATAAAGAAAGAAAGAGAGACAAGATT<br>AAG (SEQ ID NO:10) | AGCCTCATGGTCTCAT<br>(SEQ ID NO:11)        |
| LMO2        | NM_005574.2           | 1             | GGCCACAGCCCATCCA<br>(SEQ ID NO:12)            | CTTGCCCTAAATGTTCCCTTTCT<br>(SEQ ID NO:13)           | AGTAACAGCATGATTAGC<br>(SEQ ID NO:14)      |
| CD22        | NM_001771.2           | 1             | TTTGGAAGTGAGGCATTGCA<br>(SEQ ID NO:15)        | CCGGAGTCCCCAGAGTCAA<br>(SEQ ID NO:16)               | AGACGTACGTATCAGCG<br>(SEQ ID NO:17)       |
| SMN1        | NM_000344.2           | 1             | CTGGAATGTGAAGCGTTATAGAAGAT<br>(SEQ ID NO:18)  | CCTTTTCTTCCCAACACTTGA<br>(SEQ ID NO:19)             | CTGGCCTCATTTCT<br>(SEQ ID NO:20)          |
| EPDR1       | NM_017549.3           | 1             | CAGCCTCTCTTGTCCCTGGTT<br>(SEQ ID NO:21)       | TCCCTAGCAATGGACAAACTCA<br>(SEQ ID NO:22)            | CCTTATGTGTTGAATGTGG<br>(SEQ ID NO:23)     |
| CD40        | NM_001250.4           | 1             | GGGATCCTGTTGCCATCCT<br>(SEQ ID NO:24)         | GCTTCTTGGCCACCTTTTGG<br>(SEQ ID NO:25)              | TTGGTGTGTTCTTT<br>(SEQ ID NO:26)          |
| IFITM1      | NM_003641.3           | 1             | GGCTTCATAGCATTCGCCCTACT<br>(SEQ ID NO:27)     | TCACGTCGCCCAACCATCTT<br>(SEQ ID NO:28)              | CGTGAAGTCTAGGGACAG<br>(SEQ ID NO:29)      |
| VNN2        | NM_004665.2           | 1             | GACTTGATGTATGGGAGTGAGGAGT<br>T (SEQ ID NO:30) | TCTCTTCAAGGGCACAGCTATG<br>(SEQ ID NO:31)            | CAGGCCATTGCAA<br>(SEQ ID NO:32)           |
| PRPSAP<br>2 | NM_002767.2           | 1             | GCCAACTGGAACATACAGAGTGA<br>(SEQ ID NO:33)     | GCATGACGGTTCCTGTGAAA<br>(SEQ ID NO:34)              | TGCTCGGTGGGATGG<br>(SEQ ID NO:35)         |
| PRKCA       | NM_002737.2           | 1             | CGGAGGTTGAGGTTTTTTCCTT<br>(SEQ ID NO:36)      | GACGGTTGAATGGCCTCTACA<br>(SEQ ID NO:37)             | TGTATAAGCACCTACTGACA<br>AA (SEQ ID NO:38) |
| IGF1R       | NM_000875.3           | 1             | AGGACTTCTTTCATGGGTCTTACAGTT<br>(SEQ ID NO:39) | AAGTGACATTAAAGACGATGTGTATGC<br>(SEQ ID NO:40)       | TGTTAGACCATGAAACATT<br>(SEQ ID NO:41)     |
| BTG2        | NM_006763.2           | 1             | CAGGCTGTGTTCTTGCACTCTG<br>(SEQ ID NO:42)      | GACCATGAGGCTGCTTCTAATAAA<br>(SEQ ID NO:43)          | CTGCAACAGGTCCCT<br>(SEQ ID NO:44)         |
| LMO2        | NM_005574.2           | 1             | TTGGACCCCAAGGAAAACCTG<br>(SEQ ID NO:45)       | GGTTAAAAGTTGTGGTTTCCATTCTC<br>(SEQ ID NO:46)        | TGGAGACGCAATTG<br>(SEQ ID NO:47)          |
| CD22        | NM_001771.2           | 1             | GACATCCCCACTCACGAATATTATG<br>(SEQ ID NO:48)   | CTGTCTCTTTCTGGGCTTCC<br>(SEQ ID NO:49)              | CCAGTTCTGCCTCTGA<br>(SEQ ID NO:50)        |

| Gene Locus | GenBank Accession No. | Probe Overlap | Forward Primer                                 | Reverse Primer                                 | Probe                                     |
|------------|-----------------------|---------------|------------------------------------------------|------------------------------------------------|-------------------------------------------|
| SMN1       | NM_000344.2           | 1             | GGCATAGAGCAGCACTAAATGACA<br>(SEQ ID NO:51)     | TTCTATAACGCTTCACATTCAGATC<br>(SEQ ID NO:52)    | CACATAAGAAACGATCAGAC<br>(SEQ ID NO:53)    |
| EPDR1      | NM_017549.3           | 0             | CGCACTTTGGCCTTCCTAGA<br>(SEQ ID NO:54)         | TGGAAGGAGATGCAGAAAGTCAGA<br>(SEQ ID NO:55)     | CACCTGCTTCATAACCTC<br>(SEQ ID NO:56)      |
| CD40       | NM_001250.4           | 1             | CTGCCCCAGTCGGCTTCT<br>(SEQ ID NO:57)           | GTCCAAGGGTGACATTTTCG<br>(SEQ ID NO:58)         | CTCCAATGTGTATCTGTG<br>(SEQ ID NO:59)      |
| IFITM1     | NM_003641.3           | 1             | GGTTACTAGTAGCCGCCCAIA<br>(SEQ ID NO:60)        | GCAGGCCAGCATTCG<br>(SEQ ID NO:61)              | CAACCTTTGCACCTCCAC<br>(SEQ ID NO:62)      |
| VNN2       | NM_004665.2           | 1             | TGTCAATTTTGTGGCTACTCTGA<br>(SEQ ID NO:63)      | CCCAAAACACCCAGGCTCTT<br>(SEQ ID NO:64)         | CAGTGTGGAACAATG<br>(SEQ ID NO:65)         |
| PRPSAP 2   | NM_002767.2           | 0             | GTCACAGTCCCCAAGATT<br>(SEQ ID NO:66)           | CGACGGATCGCCTCTGAA<br>(SEQ ID NO:67)           | AACTGTGGATATCAGCATG<br>(SEQ ID NO:68)     |
| PRKCA      | NM_002737.2           | 0             | TGGGCAACTCAGAAATACCTCGA<br>(SEQ ID NO:69)      | ACGTCAATAGGCACGTTTGCT<br>(SEQ ID NO:70)        | CTCCCAAGATATAAGAGGC<br>(SEQ ID NO:71)     |
| IGF1R      | NM_000875.3           | 0             | GTCCACCCCTCTCCCTTTCT<br>(SEQ ID NO:72)         | CACGCACCTCTAGTACAAAGCATAAAGA<br>(SEQ ID NO:73) | CTCACTCCAAGAAAC<br>(SEQ ID NO:74)         |
| BTG2       | NM_006763.2           | 0             | CCCAACCGAATCACCTTAAGA<br>(SEQ ID NO:75)        | CAGGAGGTGGCCATCCT<br>(SEQ ID NO:76)            | ACAGGCTAGGCGAT<br>(SEQ ID NO:77)          |
| LMO2       | NM_005574.2           | 0             | TCTCATGGCATCTTCGTCTT<br>(SEQ ID NO:78)         | ATCCCTTACCCACCCCTCAA<br>(SEQ ID NO:79)         | ACTCTTAGGCACCTTGG<br>(SEQ ID NO:80)       |
| CD22       | NM_001771.2           | 0             | CGGCCTCAGGCACAAGAA<br>(SEQ ID NO:81)           | GCAGCCCATCCAGTGTCAAT<br>(SEQ ID NO:82)         | ATGTGGACTATGTGATCCT<br>(SEQ ID NO:83)     |
| SMN1       | NM_000344.2           | 0             | CATGTACATGAGTGGCTATCATACT<br>G (SEQ ID NO:84)  | GTGAGCACCTTCCTTCTTTTGA<br>(SEQ ID NO:85)       | CTATTATATGGTTTCAGAC<br>AAA (SEQ ID NO:86) |
| EPDR1      | NM_017549.3           | 0             | GACTATTGCTCTCTAAACCCAGGACT<br>A (SEQ ID NO:87) | CCAGTGCATTTAATGACCAAA<br>(SEQ ID NO:88)        | AGTCCCTCGTACTGTC<br>(SEQ ID NO:89)        |
| CD40       | NM_001250.4           | 1             | ATCAATTTTCCCGACGATCTTC<br>(SEQ ID NO:90)       | CGGTTGGCATCCATGTAAAGT<br>(SEQ ID NO:91)        | TGGCTCCAACACTG<br>(SEQ ID NO:92)          |
| IFITM1     | NM_003641.3           | 0             | AGTCCACCGTGATCAACATC<br>(SEQ ID NO:93)         | CAGGACCAGACGACATGGT<br>(SEQ ID NO:94)          | ACAGCGAGACCTCCGT<br>(SEQ ID NO:95)        |
| VNN2       | NM_004665.2           | 0             | CAACTGTGGACGGCCAGTA<br>(SEQ ID NO:96)          | GTGCCACTGAGGGAGAACATTT<br>(SEQ ID NO:97)       | AAACTGCTTCTACAAGATT<br>(SEQ ID NO:98)     |
| PRPSAP 2   | NM_002767.2           | 0             | CAGCAGAGACCCCTGAAGGAAA<br>(SEQ ID NO:99)       | CAAGCCATGAGTTGCCATCA<br>(SEQ ID NO:100)        | AGGTGCATATAAGATCTT<br>(SEQ ID NO:101)     |

| Gene Locus | GenBank Accession No. | Probe Overlap | Forward Primer                                    | Reverse Primer                                 | Probe                                       |
|------------|-----------------------|---------------|---------------------------------------------------|------------------------------------------------|---------------------------------------------|
| BCL6       | NM_001706.2           | 1             | CCCATCTCGCTCATGCTT<br>(SEQ ID NO:102)             | AATGCAGTTTAGACACAGCCAAAC<br>(SEQ ID NO:103)    | TGTTATAACTACTCCGGAGA<br>CAG (SEQ ID NO:104) |
| LRR8A      | NM_019594.2           | 1             | AGTTCAGCCAGATGGAAGGT<br>(SEQ ID NO:105)           | GCGGCATCGCTAAATAAGGA<br>(SEQ ID NO:106)        | TTCAGGGAAGTGGGC<br>(SEQ ID NO:107)          |
| BCL6       | NM_001706.2           | 1             | CACAGGGACTTGAAGTTGTTACTAAC<br>TAA (SEQ ID NO:108) | TGACGCAGAATGGGATGAGA<br>(SEQ ID NO:109)        | CTCTCTTTGGGAATGTT<br>(SEQ ID NO:110)        |
| LRR8A      | NM_019594.2           | 0             | CAAGCAGCCAGACGTTGAAC<br>(SEQ ID NO:111)           | CACACCAGATCCGGAAGACA<br>(SEQ ID NO:112)        | TTTCCCTGGGCGCAGG<br>(SEQ ID NO:113)         |
| RGS13      | NM_144766.1           | 0             | GGGATTCTTACCCAGATTCTA<br>(SEQ ID NO:114)          | CAGAAACTGTTGTTGGACTGCATAG<br>(SEQ ID NO:115)   | AGTCAGAAATGTACCAAAAA<br>(SEQ ID NO:116)     |
| YIPF3      | NM_015388.2           | 1             | TGAGCTGTAGCTGCGTAAGTACCT<br>(SEQ ID NO:117)       | GGCCTTGTCCTTTTCAGAAG<br>(SEQ ID NO:118)        | CTTGATGCCGTGCGGC<br>(SEQ ID NO:119)         |
| YIPF3      | NM_015388.2           | 1             | TGGCTGCCCTACACATGCT<br>(SEQ ID NO:120)            | CAGGATCCCTCTACCACTTG<br>(SEQ ID NO:121)        | CCTGCTCTATCTGCATTT<br>(SEQ ID NO:122)       |
| YIPF3      | NM_015388.2           | 0             | GAGGCTCAGCTGTGATTGACAT<br>(SEQ ID NO:123)         | CACCCATATCCTCGAAGCTAGAG<br>(SEQ ID NO:124)     | AGAACATGGATGATACCTC<br>(SEQ ID NO:125)      |
| RGS13      | NM_144766.1           | 0             | TCCAGCCACAGTCCCCTAGA<br>(SEQ ID NO:126)           | TCCTGAATGTTCTCTGATGATGCTCTT<br>(SEQ ID NO:127) | AGATTAACTTACAGATTCG<br>ACA (SEQ ID NO:128)  |
| EPDR1      | NM_017549.3           | 0             | CGAGGAAGCGCTGATC<br>(SEQ ID NO:129)               | ACATCACTCCATCCTTATACAGCAAA<br>(SEQ ID NO:130)  | CCTGCAAGAGATATATT<br>(SEQ ID NO:131)        |
| EPDR1      | NM_017549.3           | 0             | GGATCCTCTTGACATTCTCTCAA<br>(SEQ ID NO:132)        | GGCCCCCGATGGA<br>(SEQ ID NO:133)               | CTCCACCTTTGAAGACC<br>(SEQ ID NO:134)        |
| EPDR1      | NM_017549.3           | 0             | CGAGGTGTGCCCATATGA<br>(SEQ ID NO:135)             | GAACAGGCATTAGAAAATACCCAAAG<br>(SEQ ID NO:136)  | TGACTAGATGGCTAATATG<br>(SEQ ID NO:137)      |
| UAP1       | NM_003115.4           | 0             | CTACTGCAAGGCATGCTTTGAT<br>(SEQ ID NO:138)         | TGGCCCCCTGCATTGA<br>(SEQ ID NO:139)            | TCCCTTCATCATGCTG<br>(SEQ ID NO:140)         |
| CD79B      | NM_000626.2           | 0             | GCCGGTGCAAGTTACACGTT<br>(SEQ ID NO:141)           | CCCCAAACCCGTGACAAAC<br>(SEQ ID NO:142)         | CCTCCAAGGAGCCTC<br>(SEQ ID NO:143)          |
| CLPTM1     | NM_001294.1           | 1             | CAAGGCCCTCAACACATTCA<br>(SEQ ID NO:144)           | GGTACATAACGGGCATCTTGATG<br>(SEQ ID NO:145)     | ACCTGTTCCGCTTTG<br>(SEQ ID NO:146)          |
| UAP1       | NM_003115.4           | 1             | CCTATGCTGGAGAAGGATTAGAACT<br>(SEQ ID NO:147)      | CGATGATTAGAGGTGCATGGAA<br>(SEQ ID NO:148)      | ATGTGGCAGATAAAG<br>(SEQ ID NO:149)          |
| CD79B      | NM_000626.2           | 0             | TCTCGCCACCCTCACCAT<br>(SEQ ID NO:150)             | GCTGACAGAAGTAGATGCCATTGT<br>(SEQ ID NO:151)    | CAAGGCATCCGGTTG<br>(SEQ ID NO:152)          |

| Gene Locus | GenBank Accession No. | Probe Overlap | Forward Primer                               | Reverse Primer                               | Probe                                    |
|------------|-----------------------|---------------|----------------------------------------------|----------------------------------------------|------------------------------------------|
| CLPTM1     | NM_001294.1           | 0             | AAGTCGCCTGGAACTTCCT<br>(SEQ ID NO:153)       | CACCGAGTCCTGCTCCTCAT<br>(SEQ ID NO:154)      | ATGAGTTGTACGAGCAGTC<br>(SEQ ID NO:155)   |
| UAP1       | NM_003115.4           | 1             | CATGAGCTGCTGAAAAATGGTATTT<br>(SEQ ID NO:156) | AAAGCTATTCTCTATCGTGGCAAA<br>(SEQ ID NO:157)  | AACCAAGATACCAAGTTTT<br>(SEQ ID NO:158)   |
| CD79B      | NM_000626.2           | 1             | TCCCCAGCTCTTGCCAAAG<br>(SEQ ID NO:159)       | CAGAGAACTCCCTCCAAGTTGCT<br>(SEQ ID NO:160)   | CTGGAGTAGAAGGACAAACAG<br>(SEQ ID NO:161) |
| CLPTM1     | NM_001294.1           | 0             | GGCAGGCCAGGGTTTGT<br>(SEQ ID NO:162)         | CGAGATGGCTGGAACACAGA<br>(SEQ ID NO:163)      | AGGCGTGTCTGTC<br>(SEQ ID NO:164)         |
| CTSC       | NM_001814.3           | 1             | GACTCAGCCTCTGGGATGGA<br>(SEQ ID NO:165)      | GGATCCGGAAGTAGCCATTCT<br>(SEQ ID NO:166)     | TGGATTGTTAAAAACAGCTG<br>(SEQ ID NO:167)  |
| CTSC       | NM_001814.3           | 0             | AGCGGCTTCCATACCT<br>(SEQ ID NO:168)          | CTTCTCCACCAGCCCCAAA<br>(SEQ ID NO:169)       | ATTGCAGGAAAGTACGCC<br>(SEQ ID NO:170)    |
| CTSC       | NM_001814.3           | 0             | CCCAACCTGCACCACTGA<br>(SEQ ID NO:171)        | CAAGATGTTGGCAAAATGCAAA<br>(SEQ ID NO:172)    | CTGAAATACAGCAAAAGA<br>(SEQ ID NO:173)    |
| CD44       | NM_000610.3           | 0             | CCTTGTGGCATTTATTCATCAGT<br>(SEQ ID NO:174)   | GCTTCTATGACAAGCAGCCTTTG<br>(SEQ ID NO:175)   | AGGGTGTCGATTGG<br>(SEQ ID NO:176)        |
| PUS7       | NM_019042.3           | 0             | CTCTGTAGCACAGCTGGATTG<br>(SEQ ID NO:177)     | AGGCTGCAGTGCAAGATTGA<br>(SEQ ID NO:178)      | AGTGCATCTGCAATT<br>(SEQ ID NO:179)       |
| CD44       | NM_000610.3           | 0             | CCACTTGGAGGCTTTTCATC<br>(SEQ ID NO:180)      | AGGTGGCGATCAGGAATACA<br>(SEQ ID NO:181)      | TCGGGTGTCTATGGA<br>(SEQ ID NO:182)       |
| PUS7       | NM_019042.3           | 0             | CCTTGCCTGTTTCGATGTT<br>(SEQ ID NO:183)       | GAGCATTTCCCTGTAGGCTTCTT<br>(SEQ ID NO:184)   | CCCAAGCATAAAAAT<br>(SEQ ID NO:185)       |
| CD44       | NM_000610.3           | 0             | CAACCGTTGAAACATAACCATT<br>(SEQ ID NO:186)    | AACAATCAGTAGCACATTGCACTG<br>(SEQ ID NO:187)  | AGGAGCTGGGACACT<br>(SEQ ID NO:188)       |
| PUS7       | NM_019042.3           | 0             | TGGACTCACTGAGGCTGACGTA<br>(SEQ ID NO:189)    | GATTCGGAGAACCCCTTGATG<br>(SEQ ID NO:190)     | TCACCAAGTTTGTGAGTTC<br>(SEQ ID NO:191)   |
| RPL22      | NM_000983.3           | 1             | GCTGCCAATTTGAGCAGTTT<br>(SEQ ID NO:192)      | GTTCOCAGCTTTTCCGTTCA<br>(SEQ ID NO:193)      | TGCAAGAAAGGATCAAA<br>(SEQ ID NO:194)     |
| LOC728179  | XR_015348.1           | 1             | TCTTGCCTGCCCTGTGTTG<br>(SEQ ID NO:195)       | TGCCTTCCCCTTAATAATGCA<br>(SEQ ID NO:196)     | AAAAATCGGGTCCCTT<br>(SEQ ID NO:197)      |
| SERBP1     | NM_001018067.1        | 1             | CTCCCGTACAGAGAAGTAACAAA<br>(SEQ ID NO:198)   | AAAACATCCCTGCTACCAATACATT<br>(SEQ ID NO:199) | ATGGTAGTCAGTTTGTATT<br>(SEQ ID NO:200)   |
| RPL9       | NM_000661.4           | 1             | TCCGTTACAAGATGAGGTCTGTGT<br>(SEQ ID NO:201)  | CATTCTCTGGATAACAACGTTGA<br>(SEQ ID NO:202)   | TGCTCACTTCCCC<br>(SEQ ID NO:203)         |

| Gene Locus | GenBank Accession No. | Probe Overlap | Forward Primer                                  | Reverse Primer                                 | Probe                                     |
|------------|-----------------------|---------------|-------------------------------------------------|------------------------------------------------|-------------------------------------------|
| CFL1       | NM_005507.2           | 1             | TCCATCCCTTGACGGTTCTG<br>(SEQ ID NO:204)         | AGCCCAAGAGGAATCAAAAGATC<br>(SEQ ID NO:205)     | CCTTCCCAACTGCTTT<br>(SEQ ID NO:206)       |
| RPL13      | NM_000977.2           | 1             | GAGTCATCACTGAGGAAGAGAAGAAT<br>T (SEQ ID NO:207) | TGGCAGGGCCATACG<br>(SEQ ID NO:208)             | CAAAGCCTTCGCTAGTC<br>(SEQ ID NO:209)      |
| FLJ16025   | NM_198505.1           | 1             | CCTACACCCCTTATCCCCATACT<br>(SEQ ID NO:210)      | CCAGGGCTATTGGTTGAATGA<br>(SEQ ID NO:211)       | TTATTATCGAAACCATCAGC<br>C (SEQ ID NO:212) |
| RPS10      | NM_001014.3           | 1             | CGACCTGGGAGACTCACAAAG<br>(SEQ ID NO:213)        | GGCACAGCACTCCGTCTGT<br>(SEQ ID NO:214)         | AAGCTGACAGAGATACC<br>(SEQ ID NO:215)      |
| NPM1       | NM_002520.5           | 1             | TCTGGCTGTCCTTTTATAATGCA<br>(SEQ ID NO:216)      | CTTGGCAATAGAACCTGGACAAC<br>(SEQ ID NO:217)     | AGTGAGAACTTTCCC<br>(SEQ ID NO:218)        |
| CCDC72     | NM_015933.3           | 1             | GCAAGAAAGCCACTGAAACA<br>(SEQ ID NO:219)         | GAAAGCCTTATCTTCTCGTCCAT<br>(SEQ ID NO:220)     | CCCAAGAAGCAGGCCA<br>(SEQ ID NO:221)       |
| RPS19      | NM_001022.3           | 1             | GGCTGAAATGGTGGAAGG<br>(SEQ ID NO:222)           | CTTTGTCCCTGAGGTGTCAGTTT<br>(SEQ ID NO:223)     | CCAAGATGGCGGCGG<br>(SEQ ID NO:224)        |
| RPS16      | NM_001020.4           | 1             | TGTGGATGAGGCTTCCAAGAA<br>(SEQ ID NO:225)        | CAGCAGGTCGGTCAIAC<br>(SEQ ID NO:226)           | AGATCAAAGACATCCTCATC<br>(SEQ ID NO:227)   |
| EEF1G      | NM_001404.4           | 1             | GGCAGTGGACTACGAGTCATAC<br>(SEQ ID NO:228)       | GTCTCCTCGTGCAGGAT<br>(SEQ ID NO:229)           | CATGGCGAACTG<br>(SEQ ID NO:230)           |
| RPS5       | NM_001009.3           | 1             | CCGGAACATTAGACCATTCG<br>(SEQ ID NO:231)         | CCCTTGGCAGCATTTGAIGA<br>(SEQ ID NO:232)        | AGTGCCTGGCAGATG<br>(SEQ ID NO:233)        |
| EEF1A1     | NM_001402.5           | 1             | CTGCCACCCACTCTTAATCA<br>(SEQ ID NO:234)         | GGCCAATTGAACAAACAGTTCT<br>(SEQ ID NO:235)      | TGGTGAAGAACGGTC<br>(SEQ ID NO:236)        |
| RPL28      | NM_000991.3           | 1             | GGAAGCCTGCCACCTCCTAT<br>(SEQ ID NO:237)         | TGGCGGAGCATTCCTTG<br>(SEQ ID NO:238)           | TGCGGACCACCATC<br>(SEQ ID NO:239)         |
| ACTG1      | NM_001614.2           | 1             | TGTCCTTGAAGCTTGATCTGTATATC<br>A (SEQ ID NO:240) | TTCAATACAAGTCAAAATCAGCAA<br>(SEQ ID NO:241)    | CACTGGATTGTAGAACTT<br>(SEQ ID NO:242)     |
| BTF3       | NM_001037637.1        | 1             | AGCCTCAGATGAAAGAAACAATCA<br>(SEQ ID NO:243)     | CACCTGTGCCTGCAGTTGG<br>(SEQ ID NO:244)         | AACCAGGAAAAACTC<br>(SEQ ID NO:245)        |
| TMSB4X     | NM_021109.2           | 1             | AAGCAGGCGAATCGTAATGAG<br>(SEQ ID NO:246)        | TGCTTGTGGAATGTACAGTGCAT<br>(SEQ ID NO:247)     | CGTGCGCCGCAA<br>(SEQ ID NO:248)           |
| TPM3       | NM_153649.3           | 1             | CCCTTTCTGGGTTTGAAGCT<br>(SEQ ID NO:249)         | CTGACTGATACAAAGCACAAATTGAGA<br>(SEQ ID NO:250) | CTGTCTCTAGAAGTGCC<br>(SEQ ID NO:251)      |
| USMG5      | NM_032747.2           | 1             | GCTGTGAAGCAACATAAATGGAT<br>(SEQ ID NO:252)      | GGCATGGGAACCTTAACAGATGAG<br>(SEQ ID NO:253)    | TTAAACTGTCTACGTTCTTT<br>(SEQ ID NO:254)   |

| Gene Locus | GenBank Accession No. | Probe Overlap | Forward Primer                            | Reverse Primer                             | Probe                              |
|------------|-----------------------|---------------|-------------------------------------------|--------------------------------------------|------------------------------------|
| EIF1       | NM_005801.3           | 1             | CGCTATCCAGAACCTCCACTCT<br>(SEQ ID NO:255) | CAGGTCATCACCCCTTACTTGCA<br>(SEQ ID NO:256) | TCGACCCCTTTGCTG<br>(SEQ ID NO:257) |

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*Data Processing*

[0173] 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.  $\chi^2$  tests were used to test for associations among categorical variables.

*Normalization, Transformation and Imputation*

[0174] The following are definitions for assay data and model parameters:

**Definitions****Assay Data**

|                      |   |                                                      |
|----------------------|---|------------------------------------------------------|
| $\ell$               | = | a reference set of samples (e.g. NHL cell lines)     |
| $N_\ell$             | = | 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 $\ell$ mean of detected $\log_2$ assay values for probe $j$ (un-normalized) |
| $\hat{\sigma}_{\ell j}^{(Obs)}$  | = | set $\ell$ standard deviation of detected $\log_2$ assay values for probe $j$   |
| $\gamma_\ell^{(ND)}$             | = | set $\ell$ 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,  $\ell$ , 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

[0175] The following are definitions for assay data and model parameters:

## Definitions

### Assay Data

- $\ell$  = a reference set of samples (e.g. NHL cell lines)
- $N_\ell$  = 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  $\ell$  coefficient for probe  $j$
- $\hat{\mu}_{\ell j}$  = set  $\ell$  mean of transformed normalized assay values for probe  $j$
- $\hat{\sigma}_{\ell j}^2$  = set  $\ell$  mean of transformed normalized assay values for probe  $j$
- $C_\ell$  = 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

**[0176]** Table 11 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 11: 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 |

**[0177]** Table 12 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 12: 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. |            |                  |       |

[0178] Table 13 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 95<sup>th</sup> 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 13: 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) |

[0179] The multivariate sensitivity index is a weighted average of the probes in Tables 12 and 13. 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 14, and the association between the resulting Sensitivity Index and SPD change from baseline is depicted in Figure 7. Larger multivariate Sensitivity Index values are associated with SPD decreases post-baseline (Spearman's Rho = -0.58, P=0.006). All ranges in Tables 13, 14, and 15 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 14: 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)  |

[0180] Using 26 samples from Clinical Trail 001, ranges for  $\mu_j$  and  $\sigma_j$  values obtained are as shown in Table 15.

Table 15:  $\mu_j$  and  $\sigma_j$  ranges based on data from Clinical Trail 001

| $\mu_j$ | 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 |

| $\mu_j$ | 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 |

|            |        |      |      |      |       |      |      |      |
|------------|--------|------|------|------|-------|------|------|------|
| $\sigma_j$ | 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 |

|            |       |       |       |      |      |      |      |
|------------|-------|-------|-------|------|------|------|------|
| $\sigma_j$ | 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*

[0181] 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 16. The multivariate sensitivity index weights were taken from the 21 Clinical Trial 001 patients (Table 14), so that these patients constitute a very small validation set. 2 of 4 patients with Sensitivity Index  $\geq 0$  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 16. 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            | ?                  |

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[0182] 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 8, 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 ( $\rho=-0.23$ ).

[0183] 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.

SEQUENCE LISTING IN ELECTRONIC FORM

In accordance with Section 111(1) of the Patent Rules, this description contains a sequence listing in electronic form in ASCII text format (file: 69790-82 Seq 23-APR-10 v1.txt).

A copy of the sequence listing in electronic form is available from the Canadian Intellectual Property Office.

The sequences in the sequence listing in electronic form are reproduced in the following table.

CLAIMS:

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

(a) measuring expression level of one or more pairs of marker genes in a sample comprising B lymphoma cells obtained from said subject, wherein said one or more pairs of marker genes are selected from the group consisting of IFITM1 and BTG2, CD40 and IGF1R, RGS13 and CD44, VNN2 and CTSC, LMO2 and EPDR1, CD79B and UAP1, and CD22 and PUS7; 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 pairs of marker genes from step (a).

2. The method of claim 1, wherein the measured expression level is normalized.

3. The method of claim 1 or 2, wherein an increased expression 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 the agonist anti-CD40 antibody treatment.

4. The method of claim 3, wherein 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.

5. The method of claim 4, wherein 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.

6. The method of claim 1 or 2, wherein 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.

7. The method of claim 6, wherein 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 decreased after the anti-CD40 antibody treatment.

8. The method of claim 7, wherein 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.
9. The method of any one of claims 1-8, wherein the agonist anti-CD40 antibody stimulates CD40 and enhances the interaction between CD40 and CD40 ligand.
10. The method of claim 9, wherein 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.
11. The method of any one of claims 1-8, wherein the agonist anti-CD40 antibody stimulates CD40 and does not enhance or inhibits the interaction between CD40 and CD40 ligand.
12. The method of any one of claims 1-11, wherein the expression level of at least two, at least three, at least four, at least five, at least six, or seven pairs of marker genes are measured.
13. The method of claim 12, wherein the expression level of IFITM1 and BTG2, RGS13 and CD44, CD79B and UAP1, CD22 and PUS7, and LMO2 and EPDR1 are measured.
14. The method of any one of claims 1-13, wherein the B cell lymphoma is diffuse large B-cell lymphoma (DLBCL).
15. The method of any one of claims 1-13, wherein the B cell lymphoma is non-Hodgkin's lymphoma.
16. The method of claim 15, wherein the non-Hodgkin's lymphoma is follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, or small lymphocytic lymphoma.
17. The method of any one of claims 1-16, wherein the sample comprising the B lymphoma cells is formalin fixed paraffin embedded biopsy sample.
18. The method of any one of claims 1-17, wherein the expression level of one or more pairs of marker genes is measured by the level of an RNA transcript of the one or more pairs of marker genes.

19. The method of claim 18, wherein the RNA transcript is measured by qRT-PCR.
20. The method of any one of claims 1-17, wherein the expression level of one or more pairs of marker genes is measured by the level of the protein expression of the one or more pairs of marker genes.
21. The method of any one of claims 1-20, further comprising measuring expression level of BCL6, wherein a higher expression level of BCL6 as compared to a reference level in combination with the measured expression level of the one or more pairs of marker genes indicates that the subject is likely to respond to the anti-CD40 antibody treatment.
22. The method of any one of claims 1-3 and 6-8, further comprising measuring expression level of BCL6, wherein a higher expression level of BCL6 as compared to a reference level in combination with the measured expression level of the one or more pairs of marker genes indicates that the subject is likely to respond to the anti-CD40 antibody treatment, wherein the reference level is determined based on the expression level of BCL6 in samples comprising B lymphoma cells from subjects having tumor volume decreased after the anti-CD40 antibody treatment.
23. A method for predicting responsiveness of a subject having a B-cell lymphoma to an agonist anti-CD40 antibody treatment, comprising the steps of:
- (a) measuring the expression level of one or more pairs of marker genes in a sample comprising B lymphoma cells from the subject, wherein said one or more pairs of marker genes are selected from the group consisting of IFITM1 and BTG2, CD40 and IGF1R, RGS13 and CD44, VNN2 and CTSC, LMO2 and EPDR1, CD79B and UAP1, and CD22 and PUS7; and
- (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 (i)  $\beta_j$  is the coefficient value for each marker genes measured; (ii)  $p$  is the number of marker genes measured; (iii)  $\chi_j$  is transformed, normalized expression level for the sample from the subject for expression level of each marker measured; and (iv)  $\mu_j$  and  $\sigma_j$  are means and standard deviations for each marker gene measured; wherein  $\beta_j$ ,  $\mu_j$  and  $\sigma_j$  are determined from patient samples comprising B lymphoma cells from a clinical trial; and

wherein a value equal to 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 the anti-CD40 antibody treatment.

24. The method of claim 23, wherein the expression level of at least two, at least three, at least four, at least five, at least six, or seven pairs of marker genes are measured and used for the sensitivity index calculation.

25. The method of claim 23, wherein the expression level of IFITM1 and BTG2, RGS13 and CD44, CD79B and UAP1, CD22 and PUS7, and LMO2 and EPDR1 are measured and used for the sensitivity index calculation.

26. The method of claim 23, wherein  $\beta_j$ ,  $\mu_j$  and  $\sigma_j$  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.

27. A kit comprising reagents for measuring expression level of one or more pairs of marker genes in a sample comprising B lymphoma cells from a subject, wherein said one or more pairs of marker genes are selected from the group consisting of IFITM1 and BTG2, CD40 and IGF1R, RGS13 and CD44, VNN2 and CTSC, LMO2 and EPDR1, CD79B and UAP1, and CD22 and PUS7, wherein the kit further comprises instructions for assessing if a human subject having a B-cell lymphoma is likely to respond to an agonist anti-CD40 antibody treatment based on the expression level of said one or more pairs of markers genes.

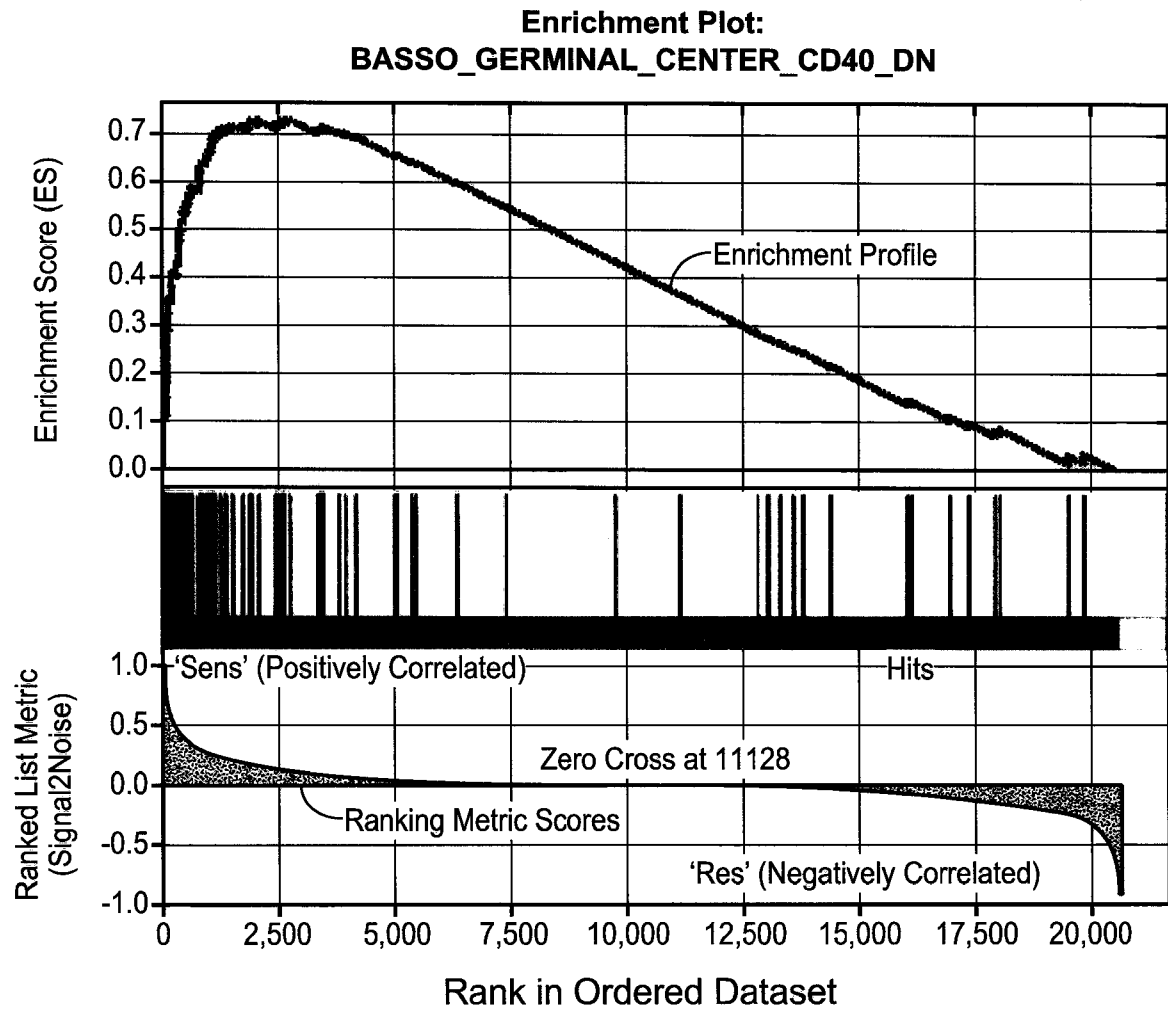
28. The kit of claim 27, wherein the reagents comprise at least a pair of primers and a probe for detecting expression level of each marker gene by qRT-PCR.

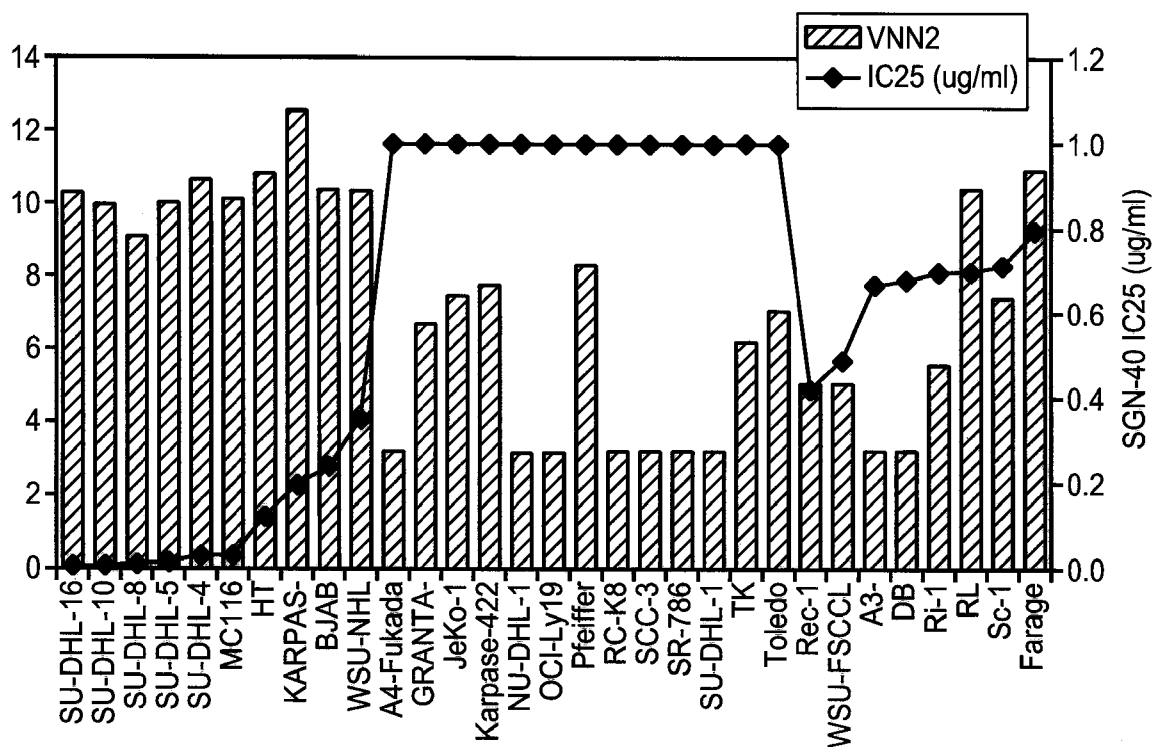
29. The kit of claim 28, wherein the sequences of said pair of primers and probe are selected from the group consisting of SEQ ID NOS:27, 28 and 29; SEQ ID NOS:60, 61, and 62; SEQ ID NOS:93, 94, and 95; SEQ ID NOS:24, 25, and 26; SEQ ID NOS:57, 58, and 59; SEQ ID NOS:90, 91 and 92; SEQ ID NOS:114, 115, 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.

30. The kit of any one of claims 27 to 29, further comprising reagents for measuring expression level of BCL6 in the sample comprising B lymphoma cells from the subject.

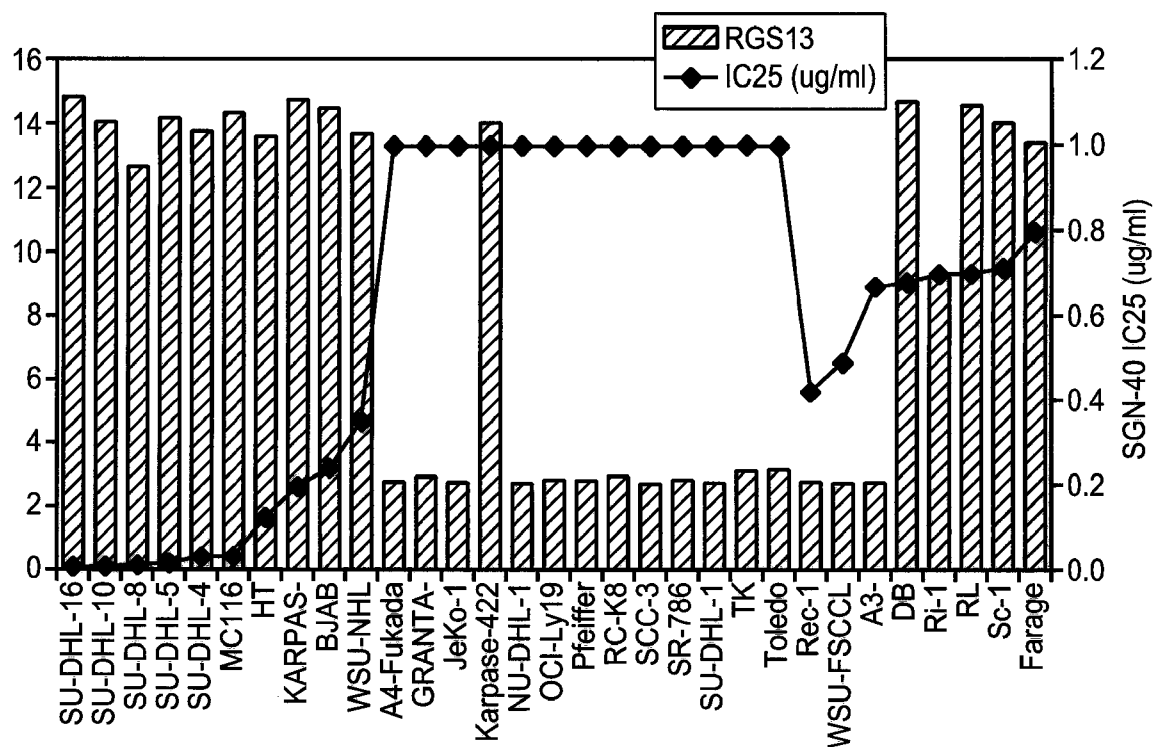
31. The kit of claim 30, wherein the reagents comprise at least a pair of primers and a probe for detecting the expression level of BCL6 by qRT-PCR.

32. The kit of claim 31, wherein the sequences of said pair of primer and probe are SEQ ID NOS:102, 103, and 104, or SEQ ID NOS:108, 109, and 110.

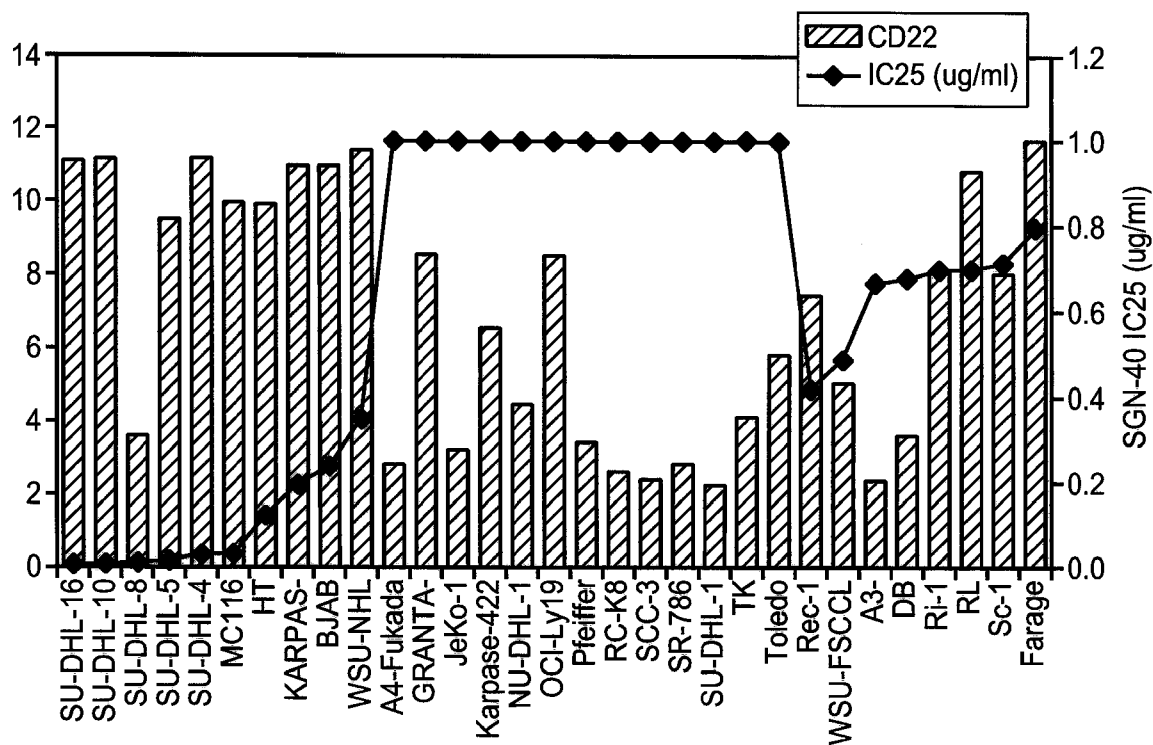
**FIG. 1**

**FIG. 2**

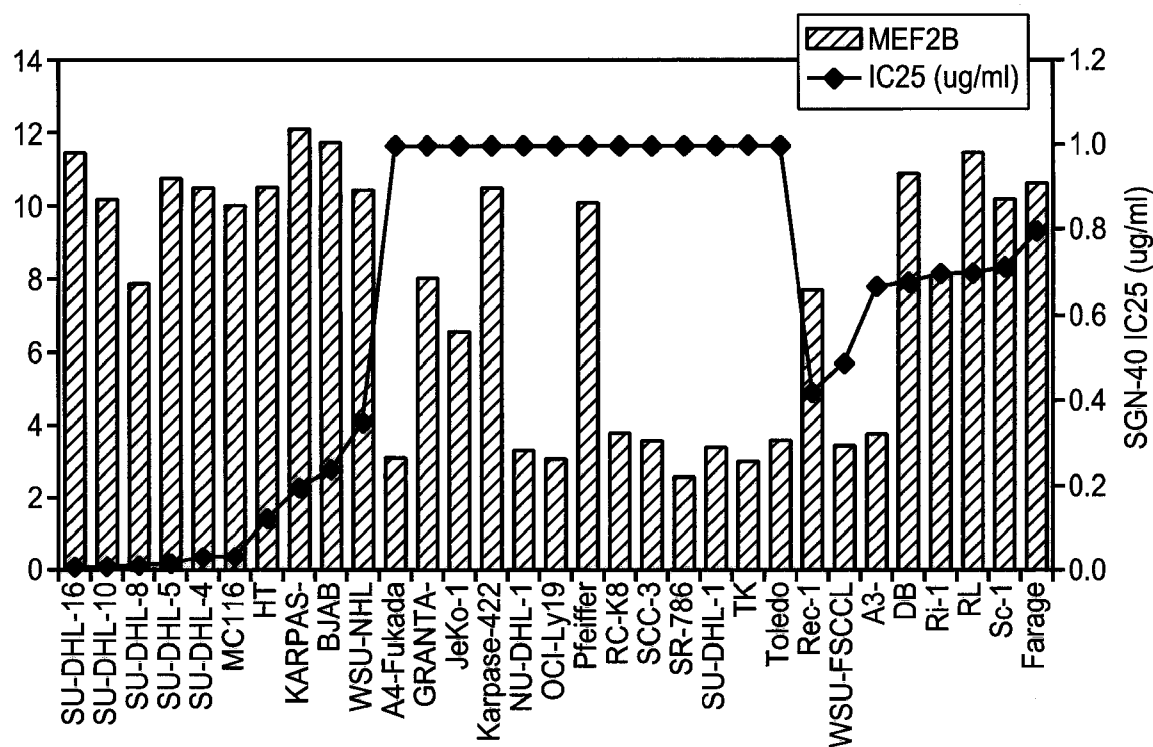
NHL Cell Lines

**FIG. 3A**

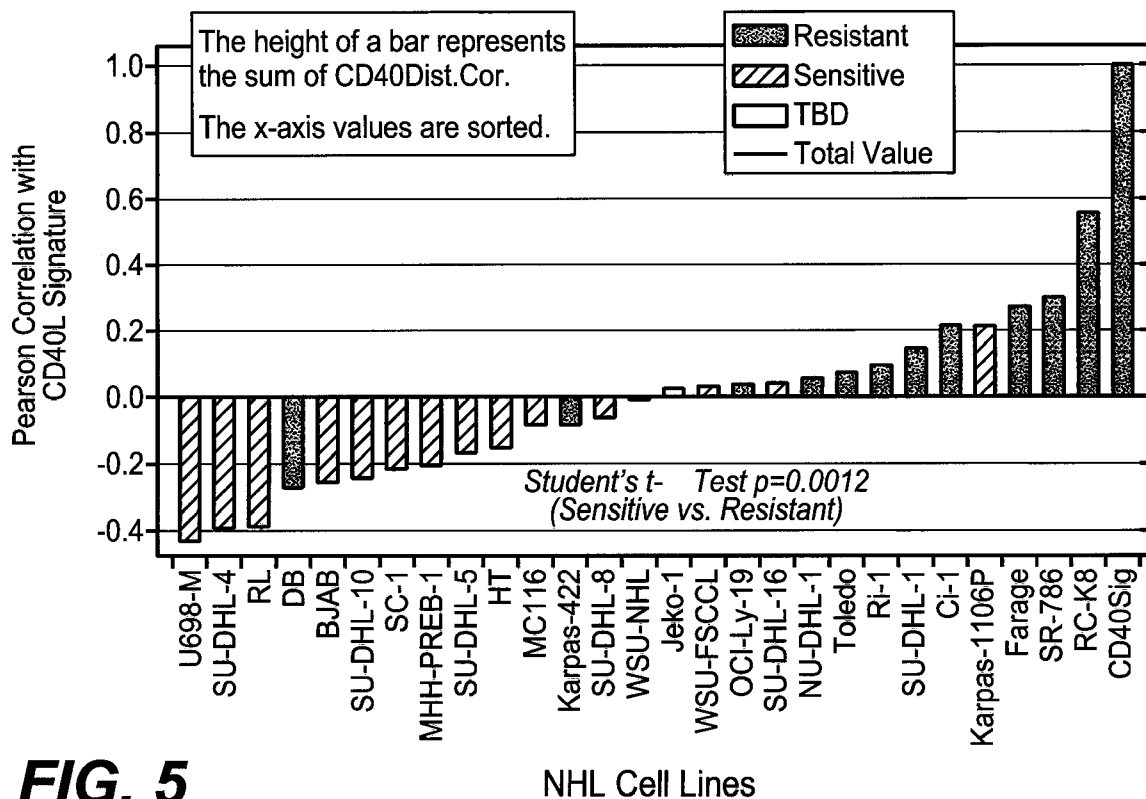
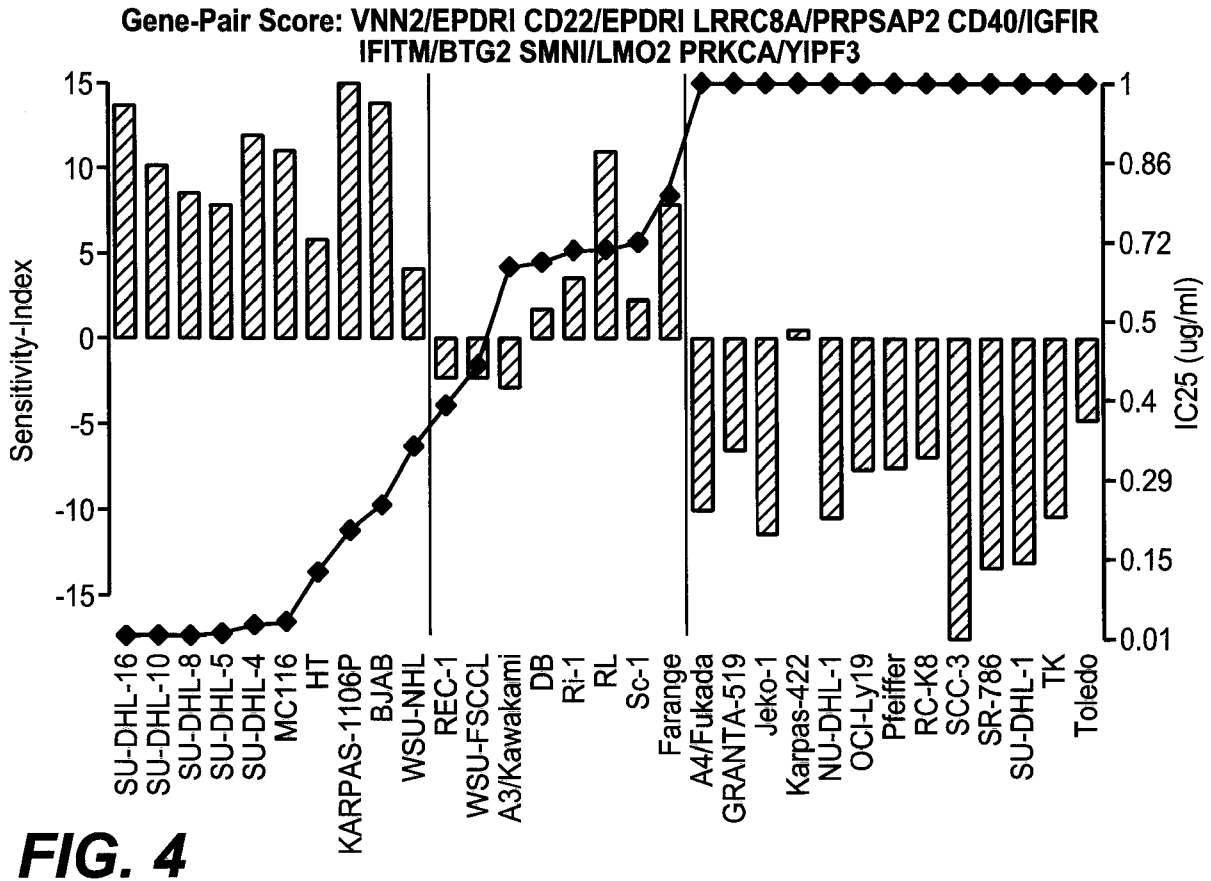
NHL Cell Lines

**FIG. 3B**

NHL Cell Lines

**FIG. 3C**

NHL Cell Lines



**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 tctctctttc caatctctgt ggcagttttt gccctaataa
61 ccctgcagggt tgggtactcag gacagtttta tagctgcagt gtatgaacat gctgtcattt
121 tgccaaataa aacagaaaaca ccagttttctc aggaggatgc cttgaatctc atgaacgaga
181 atatagacat tctggagaca gcgatcaagc aggagctga gcagggtgct cgaatcattg
241 tgactccaga agatgcactt tatggatgga aatttaccag ggaaactgtt ttcccttatac
301 tggaggatat ccagaccct cagggtgaact ggattccgtg tcaagacccc cacagatttg
361 gtcacacacc agtacaagca agactcagct gcctggccaa ggacaactct atctatgtct
421 tggcaaattt gggggacaaa aagccatgta attcccgtga ctccacatgt cctcctaattg
481 gctactttca atacaatacc aatgtggtgt ataatacaga aggaaaactc gtggcacggtt
541 accataagta ccacctgtac tctgagcctc agtttaattgt ccttgaaaag ccggagttgg
601 tgactttcaa caccgcattt ggaagggttg gcattttcac gtgctttgat atattcttct
661 atgatcctgg tgttacccctg gtgaaagatt tccatgtgga caccatactg ttcccacag
721 cttggatgaa cgttttgccc cttttgacag ctattgaatt ccattcagct tgggcaatgg
781 gaatgggagt taatcttctt gtggccaaca cacatcatgt cagcctaaat atgacaggaa
841 gtggtattta tgcaccaaag ggtcccaaag tgtatcatta tgacatgaag acagagttgg
901 gaaaacttct cttttcagag gtggattcac atcccctatc ctgcgttgcc taccacaacag
961 ctgttaattg gaatgcctac gccaccacca tcaaaccatt tccagtacag aaaaacactt
1021 tcaggggatt tatttccagg gatgggttca acttcacaga actttttgaa aatgcaggaa
1081 accttacagt ctgtcaaaag gagctttgct gtcatttaag ctacagaatg ttacaaaaag
1141 aagagaatga agtatacgtt ctaggagctt ttacaggatt acatggccga aggagaagag
1201 agtactggca ggtctgcaca atgctgaagt gcaaaaactac taatttgaca acttgtggac
1261 ggccagtaga aactgcttct acaagatttg aaatgttctc cctcagtggc acatttggaa
1321 cagagtatgt ttttcctgaa gtgctactta ccgaaattca tctgtcacct ggaaaatttg
1381 aggtgctgaa agatgggctg ttggtaaaca agaatggatc atctgggcct atactaacag
1441 tgtcactctt tgggagggtg tacacaaagg actcacttta cagctcatgt gggaccagca
1501 attcagcaat aacttacctg ctaatatcca tattattaat gatcatagct ttgcaaaata
1561 ttgtaatgtt ataggcgctc tctttatcac tcagcttctg catcatatgc ttggctgaat
1621 gtgtttatcg gcttcccaag tttactaaga aactttgaag ggctatttca gtagtataga
1681 ccagtgaagc ctaaataattt tttctcatca ataattattt ttttaagtatt atgataatgt
1741 tgtccatttt tttggctact ctgaaatgtt gcagtgtgga acaatggaaa gagcctgggt
1801 gtttgggtca gataaatgaa gatcaaaactc cagctccagc ctcatgttgc tgagactttg
1861 tgtgtatggg ggacttgtat gtatgggagt gaggagtttc agggccattg caaacatagc
1921 tgtgcccttg aagagaatag taatgatggg aatttagagg tttatgactg aattcccttt
1981 gacattaaag actatttgaa ttcaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa

```

**Figure 6-1**

# 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

```

1 gaggccagag tgccatcgaa ggtaattata gagacagtaa aatcctttta ctctgggaaa
61 aataaaatgc tgggtgtctc acaaaatttc agaacctgat ttcaaacgga tcataacaaa
121 gaggagatca aatttagcat ggtggactgc tcgacaggat atatttgtca atggaatggt
181 tccacatatt ataccaccaa catgagaaaa aaatgatcat tgtttatttg aagcttgatg
241 atattctaac gctgcctttt ctcttctcat tttagagaaa aatgagcagg cggaattggt
301 ggatttghta gatgtgcaga gatgaatcta agaggccccc ttcaaacctt actttggagg
361 aagtattaca gtgggcccag tcttttgaaa atttaatggc tacaaaatat tggatggcat
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 ttttgaagaa gctcagaaaa
661 tagtctatat gcatatggaa agggattcct accccagatt tctaaagtca gaaatgtacc
721 aaaaactttt gaaaactatg cagtccaaca acagtttctg actacaactc aaaagtttta
781 atagaaaaca gtatattgaa agtgggtggg ttgatctttt tatttagaaa cccacaaaat
841 cagaaacaca gtacaaataa aacagaaatc aaactataag ttgactttta gttcctaaaa
901 agaaacatat ttcaaaagca atggaatcta gaattcttat aacatgaata acaaaatgta
961 cagcaagcct atgtagttca attaatatat aaggaaaagg aaggcttttc ttcattgatac
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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 atgtgggttc tatattttga gatgtttttt
1441 ccttacaatg tgaactcatc gtgatcttgg aaatcaataa agtcaaatat caactaaa

```

### Figure 6-2

**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 ccatcccata gtgaggggaag acacgcggaa acaggottgc acccagacac gacaccatgc
61 atctcctcgg cccctggctc ctgctcctgg ttctagaata cttggctttc tctgactcaa
121 gtaaatgggt ttttgagcac cctgaaaccc tctacgcctg ggagggggcc tgcgtctgga
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241 ctgagtataa caagaacacc tcgaagtttg atgggacaag actctatgaa agcacaaagg
301 atgggaaggt tccttctgag cagaaaaggg tgcaattcct gggagacaag aataagaact
361 gcacactgag tatccaccgg gtgcacctca atgacagtgg tcagctgggg ctgaggatgg
421 agtccaagac tgagaaatgg atggaacgaa tacacctcaa tgtctctgaa aggccttttc
481 cacctcatat ccagctccct ccagaaattc aagagtccca ggaagtcaact ctgacctgct
541 tgctgaattt ctctgctat gggatatcga tccaattgca gtggctccta gagggggttc
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1561 agtatgcccc ccgagacgtg agggtcggga aaatcaagcc cctttccgag attcactctg
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```

**Figure 6-3**

```

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3181 aactgggtgt ggattaacct gccagggaga cagagctcac aataaaaatg gctcagatgc
3241 cacttcaaag aaaaaaaaaa

```

**Figure 6-4**

**LRRC8A**

LOCUS AY143166 2433 bp mRNA linear PRI 05-DEC-2003  
 DEFINITION Homo sapiens leucine-rich repeat-containing 8 (LRRC8) mRNA,  
 complete cds.  
 ACCESSION AY143166  
 VERSION AY143166.1 GI:27462053  
 KEYWORDS .  
 SOURCE Homo sapiens (human)

## ORIGIN

```

1 atgattccgg tgacagagct ccgctacttt gcggacacgc agccagcata ccggatcctg
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121 ttccggggga cgctgcaggt cacccaagac aagatgatct gcctgccttg taagtgggtc
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601 gtcagtggag acgtggaggc caccgtgccc atgctgcagc ggaccaagtc acggatcgag
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2281 ctgcggggca accggctgga gtgcctgcct gtggagctgg gcgagtgcct actgctcaag
2341 cgcagcggct tgggtggtgga ggaggacctg ttcaacacac tgccaccoga ggtgaaggag
2401 cggctgtgga gggctgacaa ggagcaggcc tga

```

**Figure 6-5**

**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
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241 ctgaaacgga atgccttcct tgcggtgaaa gcgaattcct agacacctgg aacagagaga
301 cacactgcca ccagcacaaa tactgcgacc ccaacctagg gcttcgggtc cagcagaagg
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901 agagacagtg aggtctgcacc caccaggagg tgtggccacg tgggcaaaca ggcagttggc
961 cagagagcct ggtgctgctg ctgctgtggc gtgaggggtga ggggctggca ctgactgggc
1021 atagctcccc gcttctgcct gcaccctgc agtttgagac aggagacctg gcactggatg
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1141 cttgtattaa agacagaggc agaagtttgg tgggtggtgg gttgggggat gggttagtaa
1201 tatccaccag accttccgat ccagcagttt ggtgcccgag gaggcacatc ggtggcttcc
1261 ctgcgcccag gaagccatat acacagatgc ccattgcagc attgtttgtg atagtgaaca
1321 actggaagct gcttaactgt ccacagcag gagactggct aaataaaatt agaatatatt
1381 tatacaacag aatctcaaaa acactgttga gtaaggaaaa aaaggcatgc tgctgaatga
1441 tgggtatgga acttttttaa aaagtacatg cttttatgta tgtatattgc ctatggatat
1501 atgtataaat acaatatgca tcatatattg atataacaag ggttctggaa gggtagacag
1561 aaaacccaca gctcgaagag tgggtgacgtc tggggtgggg aagaagggtc tggggg

```

**Figure 6-6**

**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 cagcagaaa accacacttc tcaaaccttc actcaacact tccttcccca aagccagaag
181 atgcacaagg aggaacatga ggtggctgtg ctggggggcac ccccagcac catccttcca
241 aggtccaccg tgatcaacat ccacagcgag acctccgtgc ccgaccatgt cgtctgggtc
301 ctgttcaaca ccctcttctt gaactgggtgc tgtctgggct tcatagcatt cgcctactcc
361 gtgaagtcta gggacaggaa gatggttggc gacgtgaccg gggcccaggc ctatgcctcc
421 accgccaagt gcctgaacat ctgggcccctg attctgggca tcctcatgac cattggattc
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541 gaaaaacggg gttactagta gccgccata gcctgcaacc ttgcaactcc actgtgcaat
601 gctggcccctg cacgctgggg ctgttgcccc tgcccccttg gtctgcccc tagatacagc
661 agtttatacc cacacacctg tctacagtgt cattcaataa agtgcacgtg cttgtgaaaa
721 aaaaaaaaaa aaa

```

**Figure 6-7**

# PRKCA

LOCUS NM\_002737 8787 bp mRNA linear PRI 25-SEP-2007  
 DEFINITION Homo sapiens protein kinase C, alpha (PRKCA), mRNA.  
 ACCESSION NM\_002737  
 VERSION NM\_002737.2 GI:47157319  
 KEYWORDS .  
 SOURCE Homo sapiens (human)

## ORIGIN

```

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301 gtccgggtgc ggataaggga cccgacactg atgacccag gagcaagcac aagttcaaaa
361 tccacactta cggaagcccc accttctgcg atcactgtgg gtcactgtct tatggactta
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481 atgtccccag cctctgcgga atggatcaca ctgagaagag ggggcggatt tacctaaagg
541 ctgaggttgc tgatgaaaag ctccatgtca cagtacgaga tgcaaaaaat ctaatcccta
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661 atgaaagcaa gcaaaaaacc aaaaccatcc gctccacact aaatcgcgag tggaaatgag
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2281 agtgtccagt ttaattctgt agaagttacg tctggctcta ggttaaccct tcctagaaag
2341 caagcagact gttgccccat tttgggtaca atttgatata ctttccatac cctccatctg
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```

**Figure 6-8**

```

2461 acatctccac ccaagacgtc tttggaatcc aagaacagga agccaagaga gtgagcaggg
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2581 aaacagcccc tagaatctga aaggccggga taaacctaat cactgttccc aaacattgac
2641 aaatcctaac ccaaccatgg tccagcagtt accagtttaa acaaaaaaac ctcagatgag
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```

Figure 6-9

```

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```

Figure 6-10

**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

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**Figure 6-11**

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3181 aaaaaaaaca aaaagaacaa aaaaatctgc agaaggaaaa atgtgtaatt ttgttctagt
3241 tttcagtttg tatatacccg tacaacgtgt cctcacggtg ctttttttca cggaagtttt
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3361 gttgttacta actaaactct ctttggaat gtttgtctca tcccattctg cgtcatgctt
3421 gtgttataac tactccggag acagggtttg gctgtgtcta aactgcatta ccgcttgta
3481 aaatatagct gtacaaatat aagaataaaa tgttgaaaag tcaaactgga aaaaaaa

```

**Figure 6-12**

**EPDR1**

LOCUS NM\_017549 2613 bp mRNA linear PRI 26-JUN-2007  
 DEFINITION Homo sapiens ependymin related protein 1 (zebrafish) (EPDR1), mRNA.  
 ACCESSION NM\_017549  
 VERSION NM\_017549.3 GI:116008437  
 SOURCE Homo sapiens (human)

## ORIGIN

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121 ggcagcaggc agtggcccag gcagaaatag ctcccgcgcg attcactgga gccttccccg
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```

**Figure 6-13**

**PRPSAP2**

LOCUS NM\_002767 1890 bp mRNA linear PRI 03-JUN-2007  
 DEFINITION Homo sapiens phosphoribosyl pyrophosphate synthetase-associated protein 2 (PRPSAP2), mRNA.  
 ACCESSION NM\_002767  
 VERSION NM\_002767.2 GI:22538484  
 KEYWORDS .  
 SOURCE Homo sapiens (human)

## ORIGIN

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```

**Figure 6-14**

**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

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**Figure 6-15**

20/41

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Figure 6-16

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7921 ggcctctcct ctctgtcaca tacctaccgg tttccacaac tggatttcta cagatcattc
7981 agctggttat aagggttttg tttaaactgt ccgagttact gatgtcattt tgtttttgtt
8041 ttatgtaggt agcttttaag tagaaaacac taacagtgtg gtgcccacat tagcaaatgc
8101 ttcagaaaca cctcaataaa agagaaaact tggcttgtgt gatggtgcag tcactttact
8161 ggaccaaccc acccaccttg actataccaa ggcacatct atccacagtt ctagcctaac
8221 ttcattgctga tttctctgcc tcttgatttt tctctgtgtg ttccaaataa tcttaagctg
8281 agttgtggca ttttccatgc aacctccttc tgccagcagc tcacactgct tgaagtcata
8341 tgaaccactg aggcacatca tgggaattgat gtgagcatta agacgttctc ccacacagcc
8401 cttccctgag gcagcaggag ctggtgtgta ctggagacac tgttgaactt gatcaagacc
8461 cagaccaccc caggctctct tcgtgggatg tcatgacgtt tgacatacct ttggaacgag
8521 cctcctcctt ggaagatgga agaccgtgtt cgtggccgac ctggcctctc ctggcctgtt
8581 tcttaagatg cggagtcaca tttcaatggg acgaaaagtg gcttcgtaaa atagaagagc
8641 agtcactgtg gaactaccaa atggcgagat gctcgggtgca cattgggggtg ctttgggata
8701 aaagatttat gagccaacta ttctctggca ccagattcta ggccagtttg ttccactgaa
8761 gcttttccca cagcagtcga cctctgcagg ctggcagccg aatggcttgc cagtggctct

```

Figure 6-17

```

8821 gtggcaagat cacactgaga tcgatgggtg agaaggctag gatgcttgtc tagtggttctt
8881 agctgtcacg ttggctcctt ccagggtggc cagacggtgt tggccactcc cttctaaaac
8941 acaggcgccc tcctgggtgac agtgacccgc cgtgggtatgc cttggcccat tccagcagtc
9001 ccagttatgc atttcaagtt tggggtttgt tcttttcgtt aatgttcctc tgtgttgta
9061 gctgtcttca tttcctgggc taagcagcat tgggagatgt ggaccagaga tccactcctt
9121 aagaaccagt ggcgaaagac actttcttct ttcactctga agtagctggt ggtacaaatg
9181 agaacttcaa gagaggatgt tatttagact gaacctctgt tgccagagat gctgaagata
9241 cagaccttgg acaggtcaga gggtttcatt tttggccttc atcttagatg actggttgcg
9301 tcatttggag aagtgagtgc tccttgatgg tggaatgacc ggggtggtggg tacagaacca
9361 ttgtcacagg gatcctggca cagagaagag ttacgagcag cagggtgcag ggcttggag
9421 gaatgtgggc aaggttttga acttgattgt tcttgaagct atcagaccac atcgaggctc
9481 agcagtcatc cgtgggcatt tggtttcaac aaagaaacct aacatcctac tctggaaact
9541 gatctcggag ttaaggcgaa ttgttcaaga acacaaacta catcgcatc gtcagttgtc
9601 agttctgggg catgacttta gcgttttgtt tctgagagaa cataacgatc actcattttt
9661 atgtccacag tgtgtgtgtc cgcactcttc tggtaacat tgttttaact agtcactcat
9721 tagcgttttc aatagggtct ttaagtccag tagattacgg gtagtcagtt gacgaagatc
9781 tggtttacaa gaactaatta aatgtttcat tgcatttttg taagaacaga ataattttat
9841 aaaatgtttg tagtttataa ttgccgaaaa taattttaaag acactttttt tttctctgtg
9901 tgtgcaaatg tgtgtttgtg atccattttt tttttttttt tttaggacac ctgtttacta
9961 gctagcttta caatatgcca aaaaaggatt tctccctgac cccatccgtg gttcacccctc
10021 ttttccccc atgctttttg ccctagttta taacaaagga atgatgatga tttaaaaagt
10081 agttctgtat cttcagtatc ttggtcttcc agaaccctct ggttgggaag gggatcattt
10141 tttactggtc atttcccttt ggagtgtagc tactttaaca gatggaaaga acctcattgg
10201 ccattgaaac agccgaggtg ttggagccca gcagtgcag gcaccgttcg gcactctggc
10261 tgattggtct ggttgcctgc attgtcagca cagtgccatg gacatgggaa gacttgactg
10321 cacagccaat ggttttcatg atgattacag catacacagt gatcacataa acgatgacag
10381 ctatggggca cacaggccat ttgcttacat gcctcgtatc atgactgatt actgctttgt
10441 tagaacacag aagagacctt attttattta aggcagaacc ccgaagatac gtatttccaa
10501 tacagaaaag aatttttaaa aaaaactata acatacacia aaattgggtt taaagttgac
10561 tccacttctt ctaactccag ttgattgttg gccatgtctc cccaactcca caatatctct
10621 atcatgggaa acacctgggg tttttgcgct acataggaga aagatctgga aactatttgg
10681 gttttgtttt caacttttca tttggatgtt tggcgttgca cacacacatc caccggtgga
10741 agagacgccc ggtgaaaaca cctgtctgct ttctaagcca gtgaggttga ggtgagaggt
10801 ttgccagagt ttgtctacct ctgggtatcc ctttgtctgg gataaaaaaa atcaaaccag
10861 aaggcgggat ggaatggatg caccgcaaat aatgcatttt ctgagttttc ttgttaaaaa
10921 aaaatttttt taagtaagaa aaaaaaagg aataacatgg ccaatttgtt acataaaatg
10981 actttctgtg tataaattat tcctaaaaaa tcctgtttat ataaaaaatc agtagatgaa
11041 aaaaatttca aaatgttttt gtatatcttg ttgtaagaat ttattcctgt tattgcgata
11101 tactctggat tctttacata atggaaaaaa gaaactgtct attttgaatg gctgaagcta
11161 aggcaacggt agtttctctt actctgcttt tttctagtaa agtactacat ggtttaagtt
11221 aaataaaata attctgtatg ca

```

Figure 6-18

**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

```

1  cagggtaacg ctgtcttgtg gacccgcact tcccaccga gacctctcac tgagcccgag
61  ccgcgcgcga catgagccac gggaagggaa ccgacatgct cccggagatc gccgccgccg
121  tgggcttccct ctccagcctc ctgaggaccc ggggctgcgt gagcgagcag aggccttaagg
181  tcttcagcgg ggcgctccag gaggcactca cagagcacta caaacaccac tggtttcccg
241  aaaagccgtc caagggctcc ggctaccgct gcattcgcat caaccacaag atggacccca
301  tcatcagcag ggtggccagc cagatcggac tcagccagcc ccagctgcac cagctgctgc
361  ccagcgaagt gaccctgtgg gtggaccctt atgaggtgtc ctaccgcatt ggggaggacg
421  gctccatctg cgtcttgtac gaggaggccc cactggccgc ctctgtggg ctctcacct
481  gcaagaacca agtgctgctg ggccggagca gcccctcaa gaactacgtg atggcagtct
541  ccagctaggc cctccgccc ccgccctggg cgcgcgcgtg ctcatgctgc cgtgacaaca
601  ggccaccaca tacctcaacc tggggaactg tatttttaaa tgaagagcta tttatatata
661  ttattttttt ttaagaaagg aggaaaagaa accaaaagtt tttttaaga aaaaaaatcc
721  ttcaagggag ctgcttggaa gtggcctccc caggtgcctt tggagagaac tgttgctgc
781  ttgagtctgt gagccagtgt ctgcctatag gagggggagc tgttagggg tagacctagc
841  caaggagaag tgggagacgt ttggctagca cccaggaag atgtgagagg gagcaagcaa
901  ggtagcaac tgtgaacaga gaggtcggga tttgccctgg gggaggaaga gaggccaagt
961  tcagagctct ctgtctcccc cagccagaca cctgcctccc tggctcctct attactcagg
1021  ggcattcatg cctggactta aacaatacta tgttatcttt tcttttattt ttctaataag
1081  gtcctgggca gagagtgaag aggcctctcc tgattcctac tgcctaagc tgcctttctt
1141  gaaatcatga cttgtttcta attctaccct caggggcctg tagatgttgc tttccagcca
1201  ggaatctaaa gctttgggtt ttctgagggg ggggaggagg gaactggagg ttattggggg
1261  taggatggaa gggaactctg cacaaaacct ttgctttgct agtgctgctt tgtgtgtatg
1321  tgtggcaaat aatttggggg tgatttgcaa tgaaattttg ggacccaaag agtatccact
1381  ggggatgttt tttggccaaa actcttccct ttggaaccac atgaaagtct tgatgctgct
1441  gccatgatcc ctttgagagg tggctcaaaa gctacagga actccaggtc ctttattact
1501  gccttctttt caaaagcaca actctcctct aaccctcccc tcccccttcc cttctggtcg
1561  ggtcatagag ctaccgtatt ttctaggaca agagttctca gtcactgtgc aatatgcccc
1621  ctgggtccca ggagggtctg gaggaaaact ggctatcaga acctcctgat gccctggtgg
1681  gcttagggaa ccatctctcc tgcctcctt gggatgatgg ctggctagtc agccttgcac
1741  gtattccttg gctgaatggg agagtgcctc atgttctgca agactacttg gtattcttgt
1801  agggccgaca ctaaaataaa gccaaacctt gggcactgtt ttttctccct ggtgctcaga
1861  gcacctgtgg gaaaggttgc tgtctgtctc agtacaatcc aaatttgtcg tagacttgtg
1921  caatatatac tgttgtgggt tggagaaaag tggaaagcta cactgggaag aaactccctt
1981  ccttcaattt ctacgtgaca ttgatgagg gtcccaaaa gacctcgagt ttcccaaacc
2041  gaatcacctt aagaaggaca gggctagggc atttgccag gatggccacc ctctgctgtg
2101  tgcccttag tgaggaatct tcacccact tcctctaccc ccaggttctc ctccccacag
2161  ccagtccctt ttctggatt tctaaactgc tcaattttga ctcaaaggtg ctatttacca
2221  aacactctcc ctaccattc ctgccagctc tgccctcttt tcaactctcc acattttgta
2281  ttgccttccc agacctgctt ccagtcttta ttgctttaaa gttcactttg ggccacaga
2341  cccaagagct aattttctgg tttgtgggtt gaaacaaagc tgtgaatcac tgcaggctgt
2401  gttcttgcac cttgtctgca aacaggtccc tgccttttta gaagcagcct catggtctca

```

**Figure 6-19**

24/41

2461 tgcttaatct tgtctctctt ctcttcttta tgatgttcac tttaaaaaca acaaaacccc  
2521 tgagctggac tgttgagcag gcctgtctct cctattaagt aaaaataaat agtagtagta  
2581 tgtttgtaag ctattctgac agaaaagaca aaggttacta attgtatgat agtgttttta  
2641 tatggaagaa tgtacagctt atggacaaat gtacaccttt ttgttacttt aataaaaatg  
2701 tagtaggata aaaaaaaaa

**Figure 6-20**

## 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

```

1 gaattcgtcc aaactgagga tcacaagtct ccacattctg agtaggagga tgagggtctg
61 agttaggatt tgggtcctgc agggcttgcct aaggaatccc ctgatggcct aggattccac
121 gcagagcaca tctggtgtga gagagctcgc tgcaagggtg aaggctccgc cctatcagat
181 agacaaccag gccaccaaga gggccagccc tccaaaccct ggatttgcaa catcctcaaa
241 gaacagcaac gggccttgag cagaattgag aaggaaatac cccacctgc cctcagccgt
301 taagtgggct ttgctattca caagggcctc tgggtgtcct ggcagagagg ggagatggca
361 caggcaccag gtgctagggt gccagggcct cccgagaagg aacaggtgca aagcaggcaa
421 ttagcccaag aggtatccgt ggggcaggca gcctagatct gatgggggaa gccaccagga
481 ttacatcatc tgctgtaaca actgctctga aaagaagata tttttcaacc tgaacttgca
541 gtagctagtg gagaggcagg aaaaaggaaa tgaacagag acagagggaa gcctgagcca
601 aatagacct tcccgagaga ggaggaagcc cggagagaga cgcacggctc cctccccgcc
661 cctaggccgc cgccccctct ctgccctcgg cggcgagcag ggcgcgcgca cccggggccg
721 gaaaggtgcc aggggctccg ggcggccggg cgggcgcaca ccatccccgc gggcggcgcg
781 gagccggcga cagcgcgcga gagggaccgg gcggtggcgg cggcgggacc gggatggaag
841 ggagcgcggt gactgtcctt gagcgcggag gggcgagctc gccggcgagg gccgagcaag
901 cggaggcagg agcggcggcg acggcggcgg cggcgggcgg gcccgagcac ccgagggggt
961 ccgagccccg gcagccggcc agccccgcgc caaaaaggga gcgccccgcg cgccccgcac
1021 cccgcctccc tccccaatgt cctcggccat cgaaaggaag 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 gagactatct caggcttttt gggcaagacg gtctctgcgc
1321 atcctgtgac aagcggattc gtgcctatga gatgacaatg cgggtgaaag acaaagtgt
1381 tcacctggaa tgtttcaagt gcgcgcgctg tcagaagcat ttctgtgtag gtgacagata
1441 cctcctcatc aactctgaca tagtgtgcga acaggacatc tacgagtgga ctaagatcaa
1501 tgggatgata taggcccagag tccccgggca tctttgggga ggtgttact gaagacgccg
1561 tctccatggc atcttcgtct tcaactcttag gcactttggg ggtttgaggg tggggtgagg
1621 gatttcttag gggatggtag acctttattg ggtatcaaga catagcatcc aagtggcata
1681 attcaggggc tgacacttca aggtgacaga aggaccagcc cttgagggag aacttatggc
1741 cacagcccat ccatagtaac tgacatgatt agcagaagaa aggaacattt aggggcaagc
1801 aggcgtgtg ctatcatgat ggaatttcat atctacagat agagagttgt tgtgtacaga
1861 cttgtttgtg ctttgacgct tgcgaaactag agatgtgcaa ttgatttctt ttcttctgg
1921 ctttttaact cccctgtttc aatcactgtc ctccacacaa gggaaggaca gaaaggagag
1981 tggccattct ttttttcttg gcccccttcc caaggcctta agctttggac ccaagggaaa
2041 actgcatgga gacgcatttc ggttgagaat ggaaaccaca acttttaacc aaacaattat
2101 ttaaagcaat gctgatgaat cactgttttt agacaccttc attttgaggg gaggagtcc
2161 acagattgtt tctatacaaa tataaatctt aaaaagttgt tcaactattt tattatccta
2221 gattatatca aagtatttgt cgtgtgtaga aaaaaaaaac agctctgcag gcttaataaa
2281 aatgacagac tgaaaaaaa aaaa

```

Figure 6-21

**YIPF3**

LOCUS BC019297 1554 bp mRNA linear PRI 15-JUL-2006  
 DEFINITION Homo sapiens Yip1 domain family, member 3, mRNA (cDNA clone  
 MGC:4111 IMAGE:2905449), complete cds.  
 ACCESSION BC019297  
 VERSION BC019297.1 GI:17939493  
 KEYWORDS MGC.  
 SOURCE Homo sapiens (human)

## ORIGIN

```

1  gctttctcctt tttgtgttcc ggccgatccc acctctcctc gaccctggac gtctaccttc
61  cggaggccca catcttgccc actcgcgcgc cggggctagc gcggggtttca gcgacgggag
121  ccctcaaggg acatggcaac tacagcggcg ccggcgggcg ggcgccgaaa tggagctggc
181  ccggaatggg gaggggttcga agaaaacatc cagggcggag gctcagctgt gattgacatg
241  gagaacatgg atgatacctc aggcctctagc ttcgaggata tgggtgagct gcatcagcgc
301  ctgcgcgagg aagaagtaga cgctgatgca gctgatgcag ctgctgctga agaggaggat
361  ggagagttcc tgggcatgaa gggctttaag ggacagctga gccggcagggt ggcagatcag
421  atgtggcagg ctgggaaaag acaagcctcc agggccttca gcttgtacgc caacatcgac
481  atcctcagac cctactttga tgtggagcct gctcagggtc gaagcaggct cctggagtcc
541  atgatcccta tcaagatggt caacttcccc cagaaaattg caggatgaact ctatggacct
601  ctcatgctgg tcttctactc ggttgctatc ctactccatg ggatgaagac gtctgacact
661  attatccggg agggcacctc gatgggcaca gccattggca cctgcttcgg ctactggctg
721  ggagtctcat ccttcattta ctctcttgcc tacctgtgca acgcccagat caccatgctg
781  cagatgttgg cactgctggg ctatggcctc tttgggcatt gcattgtcct gttcatcacc
841  tataatatcc acctccacgc cctcttctac ctcttctggc tgttggtggg tggactgtcc
901  aactgcgca tggtagcagt gttggtgtct cggaccgtgg gccccacaca gcggctgctc
961  ctctgtggca ccctggctgc cctacacatg ctcttctgc tctatctgca ttttgctac
1021  cacaagtgg tagaggggat cctggacaca ctggagggcc ccaacatccc gcccatccag
1081  aggggtccca gagacatccc tgccatgctc cctgctgctc ggcttcccac caccgtcctc
1141  aacgccacag ccaaagctgt tgcggtgacc ctgcagtcac actgaccca cctgaaattc
1201  ttggccagtc ctctttcccg cagctgcaga gaggaggaag actattaaag gacagtcctg
1261  atgacatgtt tcgtagatgg ggtttgcagc tgccactgag ctgtagctgc gtaagtacct
1321  ccttgatgcc tgtcggcact tctgaaaggc acaaggccaa gaactcctgg ccaggactgc
1381  aaggctctgc agccaatgca gaaaatgggt cagctccttt gagaaccctt cccacctac
1441  cccttccttc ctctttatct ctccacatt gtcttgctaa atatagactt ggtaattaaa
1501  atgttgattg aagtctggaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa

```

**Figure 6-22**

**SMN1**

LOCUS BC062723 1511 bp mRNA linear PRI 01-SEP-2006  
 DEFINITION Homo sapiens survival of motor neuron 1, telomeric, mRNA (cDNA clone MGC:72037 IMAGE:4250429), complete cds.  
 ACCESSION BC062723  
 VERSION BC062723.1 GI:38571799  
 KEYWORDS MGC.  
 SOURCE Homo sapiens (human)

## ORIGIN

```

1  ggggacccgc gggtttgcta tggcgatgag cagcggcggc agtggtggcg gcgtcccgga
61  gcaggaggat tccgtgctgt tccggcgcgg cacaggccag agcgatgatt ctgacatttg
121  ggatgataca gcaactgataa aagcatatga taaagctgtg gcttcattta agcatgctct
181  aaagaatggt gacatttggtg aaacttcggg taaaccacaa accacaccta aaagaaaacc
241  tgctaagaag aataaaagcc aaaagaagaa tactgcagct tccttacaac agtggaaagt
301  tggggacaaa tgttctgcc a tttggtcaga agacggttgc atttaccag ctaccattgc
361  ttcaattgat tttaagagag aaacctgtgt tgtggtttac actggatatg gaaatagaga
421  ggagcaaaat ctgtccgac tactttcccc aatctgtgaa gtagctaata atatagaaca
481  aaatgctcaa gagaatgaaa atgaaagcca agtttcaaca gatgaaagtg agaactccag
541  gtctcctgga aataaatcag ataacatcaa gcccaaatct gctccatgga actcttttct
601  ccctccacca ccccccacgc cagggccaa agctgggacca ggaaagccag gtctaaaatt
661  caatggccca ccaccgccac cgccaccacc accacccac ttactatcat gctggtgccc
721  tccatttcct tctggaccac caataattcc ccaccacct cccatatgtc cagattctct
781  tgatgatgct gatgctttgg gaagtatggt aatttcattg tacatgagtg gctatcatac
841  tggctattat atgggtttca gacaaaatca aaaagaagga aggtgctcac attccttaaa
901  ttaaggagaa atgctggcat agagcagcac taaatgacac cactaaagaa acgatcagac
961  agatctggaa tgtgaagcgt tatagaagat aactggcctc atttcttcaa aatatcaagt
1021  gttgggaaag aaaaaaggaa gtggaatggg taactcttct tgattaaaag ttatgtaata
1081  accaaatgca atgtgaaata ttttactgga ctctattttg aaaaaccatc tgtaaaagac
1141  tgggggtggg gtgggaggcc agcacggtgg tgaggcagtt gagaaaattt gaatgtggat
1201  tagattttga atgatattgg ataattattg gtaattttta tgagctgtga gaagggtgtt
1261  gtagtttata aaagactgtc ttaatttgca tacttaagca tttaggaatg aagtgttaga
1321  gtgtctttaa atgtttcaa tggtttaaca aaatgtatgt gaggcgtatg tggcaaaatg
1381  ttacagaatc taactggtgg acatggctgt tcattgtact gtttttttct atcttctata
1441  tgttttaaaag tatataataa aaatatttaa ttttttttta aaaaaaaaaa aaaaaaaaaa
1501  aaaaaaaaaa a

```

**Figure 6-23**

**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 cgttttcctc caaggagcct cggacgttgt cacgggtttg
61 gggtcgggga cagagcgggtg accatggcca ggctggcggt gtctcctgtg cccagccact
121 ggatggtggc gttgctgctg ctgctctcag ctgagccagt accagcagcc agatcggagg
181 accggtaccg gaatcccaaa ggtagtgtt gttcgcggt ctggcagagc ccacgtttca
241 tagccaggaa acggggcttc acggtgaaaa tgcactgcta catgaacagc gcctccggca
301 atgtgagctg gctctggaag caggagatgg acgagaatcc ccagcagctg aagctggaaa
361 agggccgcat ggaagagtcc cagaacgaat ctctcgccac cctcaccatc caaggcatcc
421 ggtttgagga caatggcatc tacttctgtc agcagaagtg caacaacacc tcggagggtc
481 accagggctg cggcacagag ctgcgagtca tgggattcag caccttggca cagctgaagc
541 agaggaacac gctgaaggat ggtatcatca tgatccagac gctgctgac atcctcttca
601 tcatcgtgcc tatcttcctg ctgctggaca aggatgacag caaggctggc atggaggaag
661 atcacacctc cgagggcctg gacattgacc agacagccac ctatgaggac atagtacgc
721 tgcggacagg ggaagtgaag tggctctgtg gtgagcacc aggccaggag tgagagccag
781 gtcgccccat gacctgggtg caggctccct ggcctcagt actgcttcg agctgcctgg
841 ctcattggcc aaccccttct ctggaccccc cagctggcct ctgaagctgg cccaccagag
901 ctgccatttg tctccagccc ctggtcccca gctcttgcca aagggcctgg agtagaagga
961 caacagggca gcaacttggg gggagttctc tggggatgga cgggaccag ccttctgggg
1021 gtgctatgag gtgatccgtc cccacacatg ggatggggga ggcagagact ggtccagagc
1081 ccgcaaattg actcggagcc gagggcctcc cagcagagct tgggaagggc catggaccca
1141 actgggcccc agaagagcca caggaacatc attcctctcc cgcaaccact cccaccccag
1201 ggaggccctg gcctccagt ccttcccccg tggataaac ggtgtgtcct gagaaaccac
1261 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa

```

**Figure 6-24**

**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 ccgaccacg tccctggcag ccccgattat ttacagcctc
121 agcagagcac ggggcggggg cagagggggc cgcccgggag ggctgctact tcttaaaacc
181 tctgcgggct gcttagtcac agccccctt gcttgggtgt gtccttcgct cgctccctcc
241 ctccgtctta ggtcactgtt ttcaacctcg aataaaaact gcagccaact tccgaggcag
301 cctcattgcc cagcggaccc cagcctctgc caggttcggg ccgccatcct cgtcccgtcc
361 tccgcccggc cctgccccgc gccaggggat cctccagctc ctttcgcccg cgccctccgt
421 tcgctccgga caccatggac aagttttggt ggcacgcagc ctggggactc tgccctcgtc
481 cgctgagcct ggcgagatc gatttgaata taacctgccg ctttgagggt gtattccacg
541 tggagaaaaa tggctgctac agcatctctc ggacggaggc cgctgacctc tgcaaggctt
601 tcaatagcac cttgccaca atggcccaga tggagaaagc tctgagcatc ggatttgaga
661 cctgcaggta tgggttcata gaagggcacg tggtgattcc ccggtccac 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 cccagcaac cctactgatg
961 atgacgtgag cagcggctcc tccagtgaag ggagcagcac ttcaggaggt tacatctttt
1021 acaccttttc tactgtacac cccatcccag acgaagacag tccctggatc accgacagca
1081 cagacagaat ccctgctacc actttgatga gcaactagtc tacagcaact gagacagcaa
1141 ccaagaggca agaaacctgg gattggtttt catggttggt tctaccatca gagtcaaaga
1201 atcatcttca cacaacaaca caaatggctg gtacgtcttc aaataccatc tcagcaggct
1261 gggagccaaa tgaagaaaat gaagatgaaa gagacagaca cctcagtttt tctggatcag
1321 gcattgatga tgatgaagat tttatctcca gcaccatttc aaccacacca cgggcttttg
1381 accacacaaa acagaaccag gactggaccc agtggaaccc aagccattca aatccggaag
1441 tgctacttca gacaaccaca aggatgactg atgtagacag aaatggcacc actgcttatg
1501 aaggaaactg gaaccagaaa gcacaccctc ccctcattca ccatgagcat catgaggaag
1561 aagagacccc acattctaca agcacaatcc aggcaactcc tagtagtaca acggaagaaa
1621 cagctaccca gaaggaacag tggtttgcca acagatggca tgagggatat cgccaaacac
1681 ccaaagaaga ctcccattcg acaacaggga cagctgcagc ctgagctcat accagccatc
1741 caatgcaagg aaggacaaca ccaagcccag aggacagttc ctggactgat ttcttcaacc
1801 caatctcaca ccccatggga cgaggtcatc aagcaggaag aaggatggat atggactcca
1861 gtcatagtat aacgcttcag cctactgcaa atccaaacac aggtttgggtg gaagatttgg
1921 acaggacagg acctctttca atgacaacgc agcagagtaa ttctcagagc ttctctacat
1981 cacatgaagg cttggaagaa gataaagacc atccaacaac ttctactctg acatcaagca
2041 ataggaatga tgtcacaggt ggaagaagag acccaaatac ttctgaaggc tcaactactt
2101 tactggaagg ttatacctct cattaccac acacgaagga aagcaggacc ttcatcccag
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 atggctgatc atcttggcat
2401 cctctttggc cttggctttg attcttgagc tttgcattgc agtcaacagt cgaagaaggt
2461 gtgggcagaa gaaaaagcta gtgatcaaca gtggcaatgg agctgtggag gacagaaagc
2521 caagtggact caacggagag gccagcaagt ctgaggaat ggtgcatttg gtgaacaagg
2581 agtcgtcaga aactccagac cagtttatga cagctgatga gacaaggaac ctgcagaatg
2641 tggacatgaa gattgggggtg taacacctac accattatct tggaaagaaa caaccgttgg

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**Figure 6-25**

```

2701 aaacataacc attacagga gctgggacac ttaacagatg caatgtgcta ctgattgttt
2761 cattgcgaat ctttttttagc ataaaaat tttt ctactctttt tgttttttgt gttttgttct
2821 ttaaagtcag gtccaatttg taaaaacagc attgctttct gaaattaggg cccaattaat
2881 aatcagcaag aatttgatcg ttccagttcc cacttggagg cctttcatcc ctcggtgtg
2941 ctatggatgg cttctaaca aaactacaca tatgtattcc tgatcgccaa cctttcccc
3001 accagctaag gacatttccc aggggttaata gggcctggtc cctgggagga aatttgaatg
3061 ggtccatttt gcccttccat agcctaattc ctgggcattg ctttccactg aggttggggg
3121 ttgggggtgta ctagttaacac atcttcaaca gacccctctc agaaattttt cagatgcttc
3181 tgggagacac ccaaaggggtg aagctattta tctgtagtaa actattttatc tgtgtttttg
3241 aaatattaaa cctggatca gtcctttgat cagtataatt ttttaaagtt actttgtcag
3301 aggcacaaaa ggggtttaaac tgattcataa taaatatctg tacttcttcg atcttcacct
3361 tttgtgctgt gattcttcag tttctaaacc agcactgtct gggccctac aatgtatcag
3421 gaagagctga gaatggtaag gagactcttc taagtcttca tctcagagac cctgagttcc
3481 cactcagacc cactcagcca aatctcatgg aagaccaagg agggcagcac tgttttgtt
3541 ttttgttttt tgtttttttt ttttgacact gtccaaagggt tttccatcct gtcctggaat
3601 cagagttgga agctgaggag cttcagcctc ttttatgggt 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 tctgtttga cttttttatg gctgtatttg taaacttaaa cacaccagtg
3901 tctgttcttg atgcagttgc tatttaggat gagttaagtg cctggggagt cctcaaaag
3961 gttaaaggga ttcccatcat tggaatctta tcaccagata ggcaagttta tgaccaaaaca
4021 agagagtaact ggcttttatcc tctaacctca tttttctcc cacttggcaa gtcctttgtg
4081 gcattttatc atcagtcagg gtgtccgatt ggctcctagaa cttccaaagg ctgcttgtca
4141 tagaagccat tgcacttata aagcaacggc tctgtttaa tggtatctcc tttctgaggc
4201 tctactaaa agtcatttgt tacctaaact tatgtgctta acaggcaatg cttctcagac
4261 caciaagcag aaagaagaag aaaagctcct gactaaatca gggctgggct tagacagagt
4321 tgatctgtag aatatcttta aaggagagat gtcaactttc tgcactatcc ccagcctctg
4381 ctctccctg tctacctctc cccctccctc tctccctcca cttcacccca caatcttgaa
4441 aaacttctct tctctctctg gaacatcatt ggccagatcc attttcagtg gtctggattt
4501 ctttttcaac ttgaaagaaa ctggacatta ggccactatg tgttgttact
4561 gccactagtg ttcaagtgc tcttgttttc ccagagattt cctgggtctg ccagaggccc
4621 agacaggctc actcaagctc tttaaactgaa aagcaacaag ccactccagg acaaggttca
4681 aaatggttac aacagcctct acctgtcgcc ccaggagaaa aggggtagtg atacaagtct
4741 catagccaga gatgggttttc cactccttct agatattccc aaaaagaggc tgagacagga
4801 gggtattttt aattttatatt tgggaattaaa tacttttttc cctttattac tgtttagtc
4861 cctcacttgg atatacctct gttttcacga tagaaataag ggaggtctag agcttctatt
4921 ccttggccat tgtcaacgga gagctggcca agtcttcaca aacccttgca acattgcctg
4981 aagtttatgg aataagatgt attctcactc ccttgatctc aagggcgtaa ctctggaagc
5041 acagcttgac tacacgtcat ttttaccat gattttcagg tgacctgggc taagtcattt
5101 aaactgggtc tttataaaag taaaaggcca acatttaatt attttgcaa gcaacctaa
5161 agctaaagat gtaatttttc ttgcaattgt aaatcttttg tgtctcctga agacttccct
5221 taaaatttagc tctgagtga aaatcaaaag agacaaaaga catcttcgaa tccatatttc
5281 aagcctggta gaattggctt ttctagcaga acctttccaa aagttttata ttgagattca
5341 taacaacacc agaattgat tttgtagcca acattcattc aatactgtta tatcagagga
5401 gtaggagaga ggaaacattt gacttatctg gaaaagcaaa atgtacttaa gaataagaat
5461 aacatgggtc attcaccttt atgttataga tatgtctttg tgtaaatacat 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 6-26

**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 agcgtctggc
61  ttccctggtaa ttcttcacct cttttctcag ctccctgcag catgggtgct gggccctcct
121  tgctgctcgc cgccctcctg ctgcttctct ccggcgacgg ccgctgctgc tgcgacacac
181  ctgccaactg cacctatctt gacctgctgg gcacctgggt cttccagggt ggctccagcg
241  gttcccagcg cgatgtcaac tgctcggtta tgggaccaca agaaaaaaaaa gtagtgggtg
301  accttcagaa gctggataca gcatatgatg accttggcaa ttctggccat ttcacccatca
361  tttaacaacca aggctttgag attgtgttga atgactacaa gtggtttgcc tttttaagt
421  ataaagaaga gggcagcaag gtgaccactt actgcaacga gacaatgact ggggtgggtgc
481  atgatgtgtt gggccggaac tgggcttgtt tcaccggaag gaaggtggga actgcctctg
541  agaattgtgt tgtcaacata gcacacctta agaattctca ggaaaagtat tctaataaggc
601  tctacaagta tgatcacaac tttgtgaaag ctatcaatgc cattcagaag tcttgactg
661  caactacata catggaatat gagactctta ccctgggaga tatgattagg agaagtgggtg
721  gccacagtcg aaaaatccca aggcccaaac ctgcaccact gactgctgaa atacagcaaa
781  agattttgca tttgccaaca tcttgggact ggagaaatgt tcatggtatc aattttgtca
841  gtcctgttcg aaaccaagca tcctgtggca gctgctactc atttgcttct atgggtatgc
901  tagaagcgag aatccgtata ctaaccaaca attctcagac cccaatccta agccctcagg
961  aggttgtgtc ttgtagccag tatgctcaag gctgtgaagg cggcttccca taccttattg
1021  caggaaagta cgcccaagat tttgggctgg tggagaagc ttgcttcccc tacacaggca
1081  ctgattctcc atgcaaaatg aaggaagact gctttcgtta ttactcctct gaggaccact
1141  atgtaggagg tttctatgga ggctgcaatg aagccctgat gaagcttgag ttggtccatc
1201  atgggccccat 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 tagggatgc
1501  cttccagtat ttcataatga tctgcatcag ttgtaaaggg gaattggtat attcacagac
1561  tgtagacttt cagcagcaat ctcagaagct tacaatatga tttccatgaa gatatttgc
1621  ttcagaatta aaactgccct taattttaat atacctttca atcgccact ggccattttt
1681  ttctaagtat tcaattaagt ggggaattttc tggagaatgg tcagctatga agtaatagag
1741  tttgcttaat catttgtaat tcaaactatgc tatatttttt aaaatcaatg tgaaaacata
1801  gacttatttt taaattgtac caatcacaag aaaataatgg caataattat caaaactttt
1861  aaaatagatg ctcatatttt taaaataaag ttttaaaaat aactgcaaaa aaaaaaaaaa
1921  aaaa

```

**Figure 6-27**

**UAP1**

LOCUS NM\_003115 2344 bp mRNA linear PRI 22-OCT-2008

DEFINITION Homo sapiens UDP-N-acteylglucosamine pyrophosphorylase 1 (UAP1), mRNA.

ACCESSION NM\_003115

VERSION NM\_003115.4 GI:156627574

```

1  cggccgcctc cgcgtccgcg tcgtcgtctg tgctcccggc gctgacgtgt ctgggcgggc
61  ggcttcact ccttcaggcg tcggcagcca ctagtcgtgg cgagaggggc ggggtggccg
121  gggctggcgc tccacttggc ccccgctccc ggcccggccc gcccgcgcg gcccgcgat
181  gaggtatat attcggagcg agcgcgggac gccgatgagt gggcgcgcgg aaggagctgg
241  agacggtcgt agctgcggtc gcgccgagaa aggtttacag gtacatacat tacacccta
301  tttctacaaa gcttggctat tagagcatta tgaacattaa tgacctcaaa ctcacgttgt
361  ccaaagctgg gcaagagcac ctactacgtt tctggaatga gcttgaagaa gcccacagg
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 gttgcataat 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 atgctccccg ccatgagttt tgatgggaaa attattttgg
961  aagagaagaa caaagtttct atgggtccag atgggaatgg tggcttttat cgggcacttg
1021  cagcccagaa tattgtggag gatatggagc aaagaggcat ttggagcatt catgtctatt
1081  gtgttgacaa catattagta aaagtggcag acccacggtt cattggattt tgcattcaga
1141  aaggagcaga ctgtggagca aagtggttag agaaaacgaa ccctacagaa ccagttggag
1201  tggtttgccg agtggatgga gtttaccagg tggtagaata tagtgagatt tccttggaac
1261  cagctcaaaa acgaagctca gacggacgac tgctgttcaa tgcggggaac attgccaacc
1321  atttcttcac tgtaccattt ctgagagatg ttgtcaatgt ttatgaacct cagttgcagc
1381  accatgtggc tcaaaagaag attccttatg tggataccca aggacagtta attaagccag
1441  acaaacccaa tggataaag atggaaaaat ttgtctttga catcttccag tttgcaaaga
1501  agtttgtggt atatgaagta ttgcgagaag atgagttttc cccactaaag aatgctgata
1561  gtcagaatgg gaaagacaac cctactactg caaggcatgc tttgatgtcc cttcatcatt
1621  gctgggtcct caatgcaggg ggccatttca tagatgaaaa tggctctcgc cttccagcaa
1681  ttccccgctt gaaggatgcc aatgatgtac caatccaatg tgaaatctct cctcttatct
1741  cctatgctgg agaaggatta gaaagtatg tggcagataa agaattccat gcacctctaa
1801  tcatcgatga gaatggagtt catgagctgg tgaaaaatgg tatttgaacc agataccaag
1861  ttttgtttgc cacgatagga atagctttta tttttgatag accaactgtg aacctacaag
1921  acgtcttggc 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 agtgtaaaaa aaaaaaaaaa
2341  aaaa

```

**Figure 6-28**

**PUS7**

LOCUS NM\_019042 3484 bp mRNA linear PRI 11-FEB-2008  
 DEFINITION Homo sapiens pseudouridylate synthase 7 homolog (S. cerevisiae)  
 (PUS7), mRNA.

ACCESSION NM\_019042 XM\_496914 XM\_499357

VERSION NM\_019042.3 GI:50727001

```

1  gtgcgagccc ggccgcccgt gagtcggctg gagcgcatct ggtcctccgc gcggaaagcg
61  ctgcttttgc ctggccgccc tagccgctgg ctcatccaag tggccttcgc cgctctcttg
121 cgtcccaacc agagcgctgg ccacctcgcc gccagctca cgcgcgccc gcgtcccag
181 gctccgggtt ttcttaaagt ttttcttgg gcttaaaga tggagatgac agaaatgact
241 ggtgtgtcgc tgaacgtgg ggactgggtt gtcgaagata atgacagtgg agtcccagtt
301 gaagagacaa aaaaacagaa gctgtcggaa tgcagtctaa ccaaaggtca agatgggcta
361 cagaatgact ttctgtccat cagtgaagac gtgcctcggc ctctgacac tgtcagtact
421 gggaaaggtg gaaagaattc tgaggctcag ttggaagatg aggaagaaga ggaggaagat
481 ggactttcag aggagtgcga ggaggaggaa tcagagagtt ttgcagacat gatgaagcat
541 ggactcactg aggtctgacgt aggcattacc aagtttgtga gttctcatca agggttctcg
601 ggaatcttaa aagaaagata ctccgacttc gttgttcatt aaataggaaa agatggacgg
661 atcagccatt tgaatgactt gtccattcca gtggatgagg aggacccttc agaagacata
721 tttacagttt tgacagctga agaaaagcag cgattggaag agctccagct gttcaaaaat
781 aaggaaacca gtgttgccat tgaggttatc gaggacacca aagagaaaag aaccatcatc
841 catcaggcta tcaaatctct gtttccagga ttagagacaa aaacagagga tagggagggg
901 aagaaatata ttgtagccta ccacgcagct gggaaaaaag ctttggcaaa tccaagaaaa
961 cattcttggc caaaatctag ggaagttac tgccacttcg tactatataa ggaaaacaaa
1021 gacaccatgg atgctattaa tgtactctcc aaatacttaa gagtcaagcc aaatatattc
1081 tcctacatgg gaaccaaaga taaaagggtc ataacagttc aagaaattgc tgttctcaaa
1141 ataactgcac aaagacttgc ccacctgaat aagtgttga tgaactttaa gctagggaat
1201 ttcagctatc aaaaaaacc actgaaattg ggagagcttc aaggaaacca cttcactgtt
1261 gttctcagaa atataacagg aactgatgac caagtacagc aagctatgaa ctctctcaag
1321 gagattggat ttattaacta ctatggaatg caaagatttg gaaccacagc tgtccctacg
1381 tatcaggttg gaagagctat actacaaaat tcctggacag aagtcattga tttaatttg
1441 aaaccccgct ctggagctga aaagggtcac ttggttaaat gcagagaaga atgggcaag
1501 accaaagacc caactgctgc cctcagaaaa ctacctgtca aaaggtgtgt ggaaggcgag
1561 ctgcttcgag gactttcaaa atatggaatg aagaatatag tctctgcatt tggcataata
1621 ccagaaata atcgcttaat gtatattcat agctaccaa gctatgtgtg gaataacatg
1681 gtaagcaaga ggatagaaga ctatggacta aaacctgttc caggggacct cgttctcaaa
1741 ggagccacag ccacctatat tgaggaagat gatgttaata attactctat ccatgatgtg
1801 gtaatgccct tgcctggttt cgatgttatt taccctaaagc ataaaattca agaagcctac
1861 agggaaatgc tcacagctga caatcttgat attgacaaca tgagacacaa aattcgagat
1921 tattccttgt caggggccta ccgaaagatc attattcgtc ctcagaatgt tagctgggaa
1981 gtcgttgcat atgatgatcc caaaattcca ctttcaaca cagatgtgga caacctagaa
2041 gggaagacac caccagtttt tgcttctgaa ggcaaataca gggctctgaa aatggatttt
2101 tctctacccc cttctactta cgccaccatg gccattcgag aagtgtctaaa aatggatacc
2161 agtatcaaga accagacgca gctgaataca acctggcttc gctgagcagt acctgttcca
2221 cagattagaa aacgtacaca agtgtttgct tcctggctcc ctgtgcattt ttgtcttagt
2281 tcagactcat atatggattt caaatctttg taataaaaat tatttgtatt tttaagtttt
2341 tattagctta aagaaataat ttgcaatatt tgtacatgta cacaaatcct gaggttctta
2401 atttttagctc agaataataa ttagtcaaaa tacacttcag gtgcttaaat cagagtaaaa
2461 tgtcagcttt acaataataa aaaaaggact ttggtttaaa gtagcaggtt taggttttgc
2521 tacattctca aaagacagca ggagtatttg acacatctgt gatggagtat acaacaatgc
2581 attttaagag caaatgcaac aaaacaaatc tggactatgg ataaataatt tgagagctgc
2641 caccacaaaa tataaatata gtactcatgc tgactgaaat aataagacat ctacaaattt

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**Figure 6-29**

```
2701 ataaacaaaa agtgattgtc attatcctgc ttatgtacta gattcaggca agcattatag
2761 acttttttggg tgcggtggct tttgcattta tattatcaat gccttgcagg aacgttgcac
2821 tgataggccc attttatttt tttatttttt ttttcgagac aggatctcac tctgtagcac
2881 aggctggatt gcagtgcaat cctgcaattc tcaatcttgc actgcagcct cgacctccca
2941 ggctccagtg actctcccac ctcagcctcc taagtagctg ggagtacagg cgcgaccac
3001 cacgcctagc tgatttttgt atttttttgt agagacgggg gtttggccat gttgccgagg
3061 ctaactcctg ggattacagg catgagctgt gctggccggg ttttttttct ttgatgtaaa
3121 cgtgtacagc tgttttatta gttaaggctc aatttttact ctaggtgcct tttatgttca
3181 gaactctttc cactggactg gtatttgctc aaaaataaat aatggtagag aagaaaacta
3241 taaaaatgga caaggctttc ttctatcagt agcgtttacc ctttgtcacc agtggctttg
3301 gtattttccat gtctggcatt gcataaaactt ctctggtgtg aaaggataaa tatgcctttc
3361 taaagttgta tatcaaaatt gtatcaattt ttatttttcta tgatttctag aaacaaatgt
3421 aataaatatt tttaaaatct cctttctact ggttatgtaa ataaatcaaa taaatatatc
3481 aaaa
```

**Figure 6-30**

**RGS 13**

LOCUS NM\_002927 1498 bp mRNA linear PRI 10-FEB-2008  
 DEFINITION Homo sapiens regulator of G-protein signaling 13 (RGS13),  
 transcript variant 1, mRNA.  
 ACCESSION NM\_002927  
 VERSION NM\_002927.3 GI:21464137

```

1 gaggccagag tgccatcgaa ggtaattata gagacagtaa aatcctttta ctctgggaaa
61 aataaaatgc tgggtgtctc acaaaatttc agaacctgat ttcaaacgga tcataacaaa
121 gaggagatca aatttagcat ggtggactgc tcgacaggat atatttgtca atggaatggt
181 tccacatatt ataccaccaa catgagaaaa aaatgatcat tgtttatttg aagcttgatg
241 atattctaac gctgcctttt ctcttctcat ttagagaaaa aatgagcagg cggaattggt
301 ggatttgtaa gatgtgcaga gatgaatcta agaggccccc ttcaaacctt actttggagg
361 aagtattaca gtgggcccag tcttttgaaa atttaatggc tacaaaatat ggtccagtag
421 tctatgcagc atatttaaaa atggagcaca gtgacgagaa tattcaattc tggatggcat
481 gtgaaaccta taagaaaatt gcctcacggt ggagcagaat ttctagggca aagaagcttt
541 ataagattta catccagcca cagtccccta gagagattaa cattgacagt tcgacaagag
601 agactatcat caggaacatt caggaaccca ctgaaacatg ttttgaagaa gctcagaaaa
661 tagtctatat gcatatggaa agggattcct accccagatt tctaaagtca gaaatgtacc
721 aaaaactttt gaaaactatg cagtccaaca acagtttctg actacaactc aaaagtttaa
781 atagaaaaca gtatattgaa agtgggtgggt ttgatctttt tatttagaaa cccacaaaat
841 cagaaacaca gtacaaataa aacagaaatc aaactataag ttgactttta gttcctaaaa
901 agaaacatat ttcaaaagca atggaatcta gaattcttat aacatgaata acaaaatgta
961 cagcaagcct atgtagttca attaatatat aaggaaaagg aaggcttttc ttcattgatac
1021 aagcattata aagtttttac tgtagtagtc aattaatgga ttttccttg 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 ttaacaaaact tctttatcac atgtatcttc
1321 tacatgtaaa acatttctga tgatttttta acaaaaaata tatgaatttc ttcatttgct
1381 cttgcatcta cattgctata aggatataaa atgtggtttc tatattttga gatgtttttt
1441 ccttacaatg tgaactcatc gtgatcttgg aaatcaataa agtcaaatat caactaaa

```

**Figure 6-31**

**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

```

1 cttttgctct cagatgctgc caggggtccct gaagagggaa gacacgcgga aacaggcttg
61 cccccagaca cgacaccatg catctcctcg gcccctggct cctgctcctg gttctagaat
121 acttggtctt ctctgactca agtaaatggg tttttgagca ccctgaaacc ctctacgcct
181 gggagggggc ctgcgtctgg atccccctgca cctacagagc cctagatggg gacctggaaa
241 gcttcacatc gttccacaat cctgagtata acaagaacac ctggaagttt gatgggacaa
301 gactctatga aagcacaaag gatgggaagg ttcttctga gcagaaaagg gtgcaattcc
361 tgggagacaa gaataagaac tgcacactga gtatccaccc ggtgcacctc aatgacagtg
421 gtcagctggg gctgaggatg gagtccaaga ctgagaaatg gatggaacga atacacctca
481 atgtctctga aaggcctttt ccacctcata tccagctccc tccagaaatt caagagtccc
541 aggaagtac tctgacctgc ttgtgaatt tctcctgcta tgggtatccg atccaattgc
601 agtggctcct agaggggggt ccaatgaggc aggtctgtgt cacctcgacc tcttgacca
661 tcaagtctgt cttcacccgg agcagactca agttctcccc acagtggagt caccatggga
721 agattgtgac ctgccagctt caggatgcag atgggaagtt cctctccaat gacacggtgc
781 agctgaacgt gaagcacacc ccgaagttgg agatcaaggt cactccagat gatgccatag
841 tgagggaggg ggactctgtg accatgacct gcgaggtcag cagcagcaac ccggagtaca
901 cgaaggatc ctggctcaag gatgggacct cgctgaagaa gcagaatata ttcacgctaa
961 acctgcgcga agtgaccaag gaccagagtg ggaagtactg ctgtcaggtc tccaatgacg
1021 tgggcccggg aagggtcggaa gaagtgttcc tgcaagtgca gtatgccccg gaaccttcca
1081 cgggttcagat cctccactca ccggctgtgg aggggaagtca agtcgagttt ctttgcatgt
1141 cactggccaa tcctottcca acaaattaca cgtggtacca caatgggaaa gaaatgcagg
1201 gaaggacaga ggagaaagtc cacatcccaa agatcctccc ctggcacgct gggacttatt
1261 cctgtgtggc agaaaacatt cttggtactg gacagagggg cccgggagct gagctggatg
1321 tccagtatcc tccaagaag gtgaccacag tgattcaaaa ccccatgccg attcgagaag
1381 gagacacagt gaccttttcc tgtaaactaca attccagtaa cccagtggtt acccggtatg
1441 aatggaaacc ccatggcgcc tgggaggagc catcgcttgg ggtgctgaag atccaaaacg
1501 ttggtctggg caacacaacc atcgctgccc cagcttghta tagttggtgc tegtgggcct
1561 cccctgtcgc cctgaatgtc cagtatgcc cccgagacgt gagggtccgg aaaatcagc
1621 ccccttccga gattcactct ggaaactcgg tcagcctcca atgtgacttc tcaagcagcc
1681 accccaaaga agtccagttc ttctgggaga aaaatggcag gcttctgggg aaagaaagcc
1741 agctgaattt tgactccatc tccccagaag atgctgggag ttacagctgc tgggtgaaca
1801 actccatagg acagacagcg tccaaggcct ggacacttga agtgctgtat gcaaccagga
1861 ggctgcgtgt gtccatgagc ccgggggacc aagtgatgga ggggaagagt gcaacctga
1921 cctgtgagag cgacgccaac cctccgctct ccactacac ctggtttgac tgggaataacc
1981 aaagcctccc ctaccacagc cagaagctga gattggagcc ggtgaaggtc cagcactcgg
2041 gtgcctactg gtgccagggg accaacagtg tgggcaaggg ccgttcgcct ctcagcacc
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2161 gcctcgccat cctcatcctg gcaatctgtg ggctcaagct ccagcgacgt tggagagga
2221 cacagagcca gcaggggctt caggagaatt ccagcgcca gagcttcttt gtgaggaata
2281 aaaaggtag aaggggcccc ctctctgaag gccccactc cctgggatgc tacaatccaa
2341 tgatggaaga tggcattagc tacaccaccc tgcgttttcc cgagatgaac ataccacgaa
2401 ctggagatgc agagtctca gagatgcaga gacctcccc ggactgcgat gacacggtca
2461 cttattcagc attgcacaag cgccaagtgg gcgactatga gaacgtcatt ccagattttc
2521 cagaagatga ggggattcat tactcagagc tgatccagtt tggggtcggg gagcggcctc
2581 aggcacaaga aaatgtggac tatgtgatcc tcaaacattg aactggatg ggctgcagca
2641 gaggcactgg gggcagcggg ggccagggaa gtccccagat ttccccagac accgccacat

```

**Figure 6-32**

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```
2701 ggcttcctcc tgcgcgcatg tgcgcacaca cacacacaca cgcacacaca cacacacaca
2761 ctcaactgogg agaaccttgt gcctgggtca gagccagtct ttttggtgag ggtaacccca
2821 aacotccaaa actcctgccc ctgttctctt ccactctcct tgctaccag aaatccatct
2881 aaatacctgc cctgacatgc acacotcccc ctgccccac cagggccact ggccatctcc
2941 acccccagct gcttgtgtcc ctccctgggat ctgctcgtca tcatttttcc ttcccttctc
3001 catctctctg gccctctacc cctgatctga catccccact caggaatatt atgccagtt
3061 tctgcctctg agggaaagcc cagaaaagga cagaaacgaa gtagaaaggg gccagtcct
3121 ggccctggctt ctcccttgga agtgaggcat tgcacgggga gacgtacgta tcagcggccc
3181 cttgactctg gggactccgg gtttgagatg gacacactgg tgtggattaa cctgccaggg
3241 agacagagct cacaataaaa atggctcaga tgccacttca aagaaaaaaa aaa
```

**Figure 6-33**

**SMN 1**

LOCUS NM\_000344 1621 bp mRNA linear PRI 10-AUG-2008  
 DEFINITION Homo sapiens survival of motor neuron 1, telomeric (SMN1),  
 transcript variant d, mRNA.  
 ACCESSION NM\_000344 XM\_001126655  
 VERSION NM\_000344.2 GI:13259515

```

1 ccacaaatgt gggagggcga taaccactcg tagaaagcgt gagaagttac tacaagcggg
61 cctcccggcc accgtactgt tccgctccca gaagccccgg gcggcggaag tcgtcactct
121 taagaaggga cggggcccca cgctgcgcac ccgcgggttt gctatggcga tgagcagcgg
181 cggcagtggg ggcggcgtcc cggagcagga ggattccgtg ctgttccggc gcggcacagg
241 ccagagcgat gattctgaca tttgggatga tacagcactg ataaaagcat atgataaagc
301 tgtggcttca ttttaagcatg ctctaaagaa tggtgacatt tgtgaaactt cgggtaaacc
361 aaaaaccaca ctaaaaagaa aacctgctaa gaagaataaa agccaaaaga agaatactgc
421 agcttcctta caacagtggg aagttgggga caaatgttct gccatttggg cagaagacgg
481 ttgcatttac ccagctacca ttgcttcaat tgattttaag agagaaacct gtgttgtggt
541 ttacactgga tatggaaata gagaggagca aaatctgtcc gatctacttt cccaatctg
601 tgaagtagct aataatatag aacagaatgc tcaagagaat gaaaatgaaa gccaaagtct
661 aacagatgaa agtgagaact ccaggtctcc tggaaataaa tcagataaca tcaagcccaa
721 atctgctcca tggaaactct ttctccctcc accaccccc atgccagggc caagactggg
781 accaggaaag ccaggtctaa aattcaatgg ccaccaccg ccaccgccac caccaccacc
841 ccacttacta tcatgctggc tgctccatt tccttctgga ccaccaataa ttccccacc
901 acctccata tgtccagatt ctcttgatga tgctgatgct ttgggaagta tgttaatttc
961 atggtacatg agtggctatc atactggcta ttatatgggt ttcagacaaa atcaaaaaga
1021 aggaaggtgc tcacattcct taaattaagg agaaatgctg gcatagagca gactaaatg
1081 acaccactaa agaaacgatc agacagatct ggaatgtgaa gcgttataga agataactgg
1141 cctcatttct tcaaaatata aagtgttggg aaagaaaaaa ggaagtggaa tgggtaactc
1201 ttcttgatta aaagttatgt aataaccaa tgcaatgtga aatattttac tggactcttt
1261 tgaaaaacca tctgtaaaag actgggggtg ggggtgggagg ccagcacggg ggtgaggcag
1321 ttgagaaaat ttgaatgtgg attagatatt gaatgatatt ggataattat tggtaatttt
1381 atggcctgtg agaagggtgt tgtagtttat aaaagactgt ctttaatttg atacttaagc
1441 atttaggaat gaagtgttag agtgtcttaa aatgtttcaa atggtttaac aaaatgtatg
1501 tgaggcgtat gtggcaaaat gttacagaat ctaactgggt gacatggctg ttcattgtac
1561 tgtttttttc tatcttctat atgtttaaaa gtatataata aaaatattta attttttttt
1621 a

```

**Figure 6-34**

**YIPF 3**

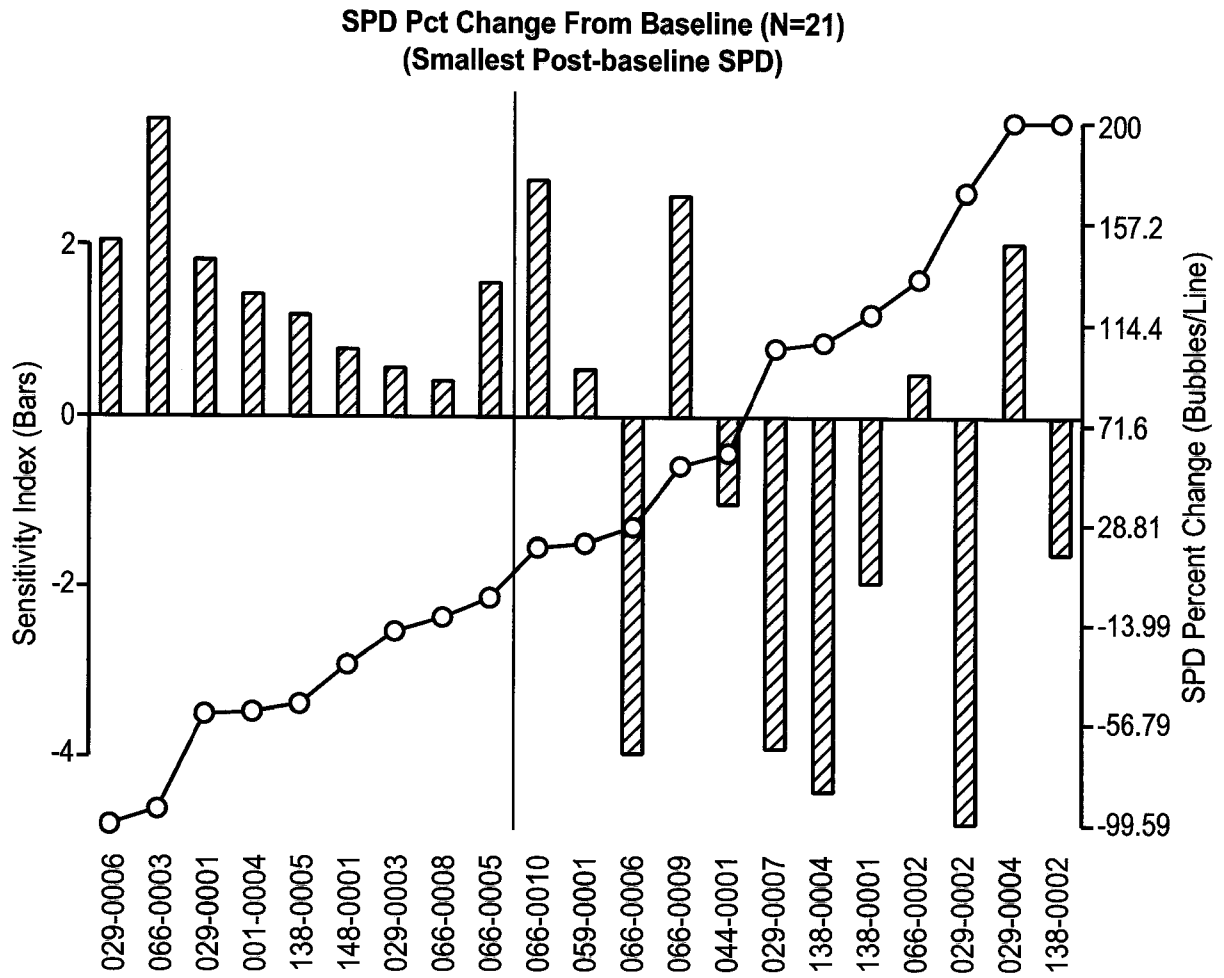
LOCUS NM\_015388 1572 bp mRNA linear PRI 28-SEP-2008  
 DEFINITION Homo sapiens Yip1 domain family, member 3 (YIPF3), mRNA.  
 ACCESSION NM\_015388  
 VERSION NM\_015388.2 GI:49472827

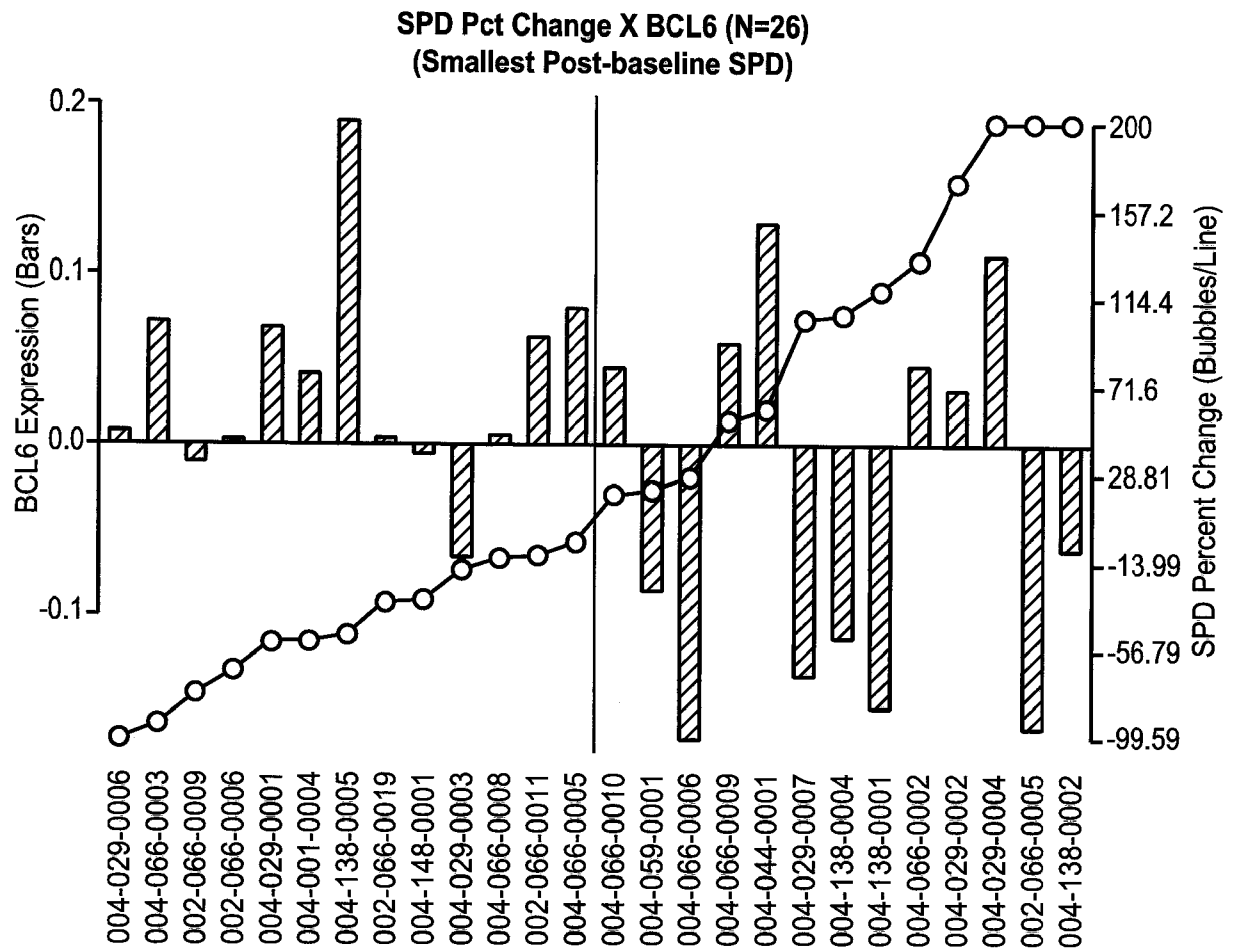
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1 aagttgcttt tgtccaaaca tccgggcttc tcctttttgt gttccggccg atcccacctc
61 tcctcgaccc tggacgtcta ccttccggag gccacatct tgcccactcc gcgcgcgggg
121 ctagcgcggg ttccagcgac gggagccctc aagggacatg gcaactacag cggcgccggc
181 gggcggcgcc cgaaatggag ctggcccggg atggggaggg ttcgaagaaa acatccaggg
241 cggaggctca gctgtgattg acatggagaa catggatgat acctcaggct ctagcttcga
301 ggatatgggt gagctgcatc agcgcctgcg cgaggaagaa gtagacgctg atgcagctga
361 tgcagctgct gctgaagagg aggatggaga gttcctgggc atgaagggct ttaagggaca
421 gctgagccgg caggtggcag atcagatgtg gcaggctggg aaaagacaag cctccagggc
481 cttcagcttg tacgccaaca tcgacatcct cagaccctac tttgatgtgg agcctgtcga
541 ggtgcgaagc aggtccttg agtccatgat ccctatcaag atggtcaact tccccagaa
601 aattgcagggt gaactctatg gacctctcat gctggctctt actctggttg ctatcctact
661 ccatgggatg aagacgtctg acactattat ccgggagggc accctgatgg gcacagccat
721 tggcacctgc ttcggtact ggctgggagt ctcatccttc atttacttcc ttgcctacct
781 gtgcaacgcc cagatcacca tgctgcagat gttggcactg ctgggctatg gcctctttgg
841 gcattgcatt gtcctgttca tcacctataa tatccacctc cacgccctct tctacctctt
901 ctggctgttg gtgggtggac tgtccacact gcgcatggta gcagtgttgg tgtctcggac
961 cgtgggcccc acacagcggc tgctcctctg tggcaccctg gctgccctac acatgctctt
1021 cctgctctat ctgcattttg cctaccacaa agtggtagag gggatcctgg acacactgga
1081 gggccccaac atcccgcca tccagagggg cccagagac atccctgcca tgctccctgc
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1201 gtcacactga cccacctga aattcttggc cagtcctctt tcccgcagct gcagagagga
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1321 ctgagctgta gctgcgtaag tacctccttg atgcctgtcg gcacttctga aaggcacaag
1381 gccagaact cctggccagg actgcaaggc tctgcagcca atgcagaaaa tgggtcagct
1441 cctttgagaa cccctcccca cctaccctt ccttcctctt tatctctccc acattgtctt
1501 gctaaatata gacttggtaa ttaaaatgtt gattgaagtc tgggaactgca aaaaaaaaaa
1561 aaaccaaaaa aa

```

**Figure 6-35**

**FIG. 7**

**FIG. 8**