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

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

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, which application is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present invention relates generally to the fields of predicting, assessing, aiding assessment of responsiveness of 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+ T cells.

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

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

(ADCC) and antibody-dependent cellular phagocytosis (ADCP). In vivo, using xenograft models of multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL), the anti-CD40 antibody suppresses tumor growth and improves survival in severe combined immunodeficient (SCID) mice. Comparison of the anti-CD40 antibody to rituximab (Genentech, Inc.) in several models revealed anti-tumor activity of the anti-CD40 antibody was at least as effective as rituximab.

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

[0008a] It is to be understood that, if any prior art publication is referred to herein, such reference does not

constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

SUMMARY OF THE INVENTION

[0009] The invention relates to 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.

A first aspect provides a method for predicting 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 FITM1, 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).

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

(a) measuring expression level of marker genes in a sample comprising B lymphoma cells obtained from said subject, wherein said marker genes are CD40 and one or more genes selected from the group consisting of FITM1, 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 CD40 and said one or more marker genes from step (a).

A third aspect provides a method of treating a subject having B-cell lymphoma comprising the steps of:

(a) measuring expression level of one or more marker genes selected from the group consisting of FITMI, 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;

(b) generating a report summarizing the expression level of one or more marker genes obtained in step (a); and

(c) administering an effective amount of an anti-CD40 antibody to the subject if the subject is predicted to be likely to respond to the anti-CD40 antibody treatment based on the measured expression level of the one or more marker genes provided in the report of step (b).

A fourth aspect provides a method of treating a subject having B-cell lymphoma comprising the steps of:

(a) measuring expression level of marker genes in a sample comprising B lymphoma cells obtained from said subject, wherein said marker genes are CD40 and one or more genes selected from the group consisting of FITM1, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7;

(b) generating a report summarizing the expression level of one or more marker genes obtained in step (a); and

(c) administering an effective amount of an anti-CD40 antibody to the subject if the subject is predicted to be likely to respond to the anti-CD40 antibody treatment based on the measured expression level of CD40 and said one or more marker genes provided in the report of step (b).

A fifth aspect provides a method for predicting 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 FITM1, 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) β_j is the coefficient value for each marker genes measured; (ii) p is the number of marker genes measured; (iii) x_j is transformed, normalized expression level for the sample from the subject for expression level of each marker measured; and (iv) μ_j and σ_j are means and standard deviations for each marker gene measured; wherein β_j, μ_j and σ_j are determined from patient samples comprising B lymphoma cells from a clinical trial; and

wherein 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.

A sixth aspect provides a kit when used in the method of

any one of the first, third or fifth aspects, the kit comprising reagents for measuring expression level of at least one marker gene selected from the group consisting of FITM1, CD79B, IGFIR, CD44, CTSC, EPDR1, PUS7, RGS13, VNN2, LM02, CD22, BTG2, and UAP1 in a sample comprising B lymphoma cells from a subject.

A seventh aspect provides a kit when used in the method of any one of the second, fourth or fifth asepects, the kit comprising reagents for measuring expression level of at least two marker genes, wherein the marker genes are CD40 and one or more marker genes selected from the group consisting of FITM1, CD79B, IGFIR, CD44, CTSC, EPDR1, PUS7, RGS13, VNN2, LM02, CD22, BTG2, and UAP1 in a sample comprising B lymphoma cells from a subject.

An eighth aspect provides use of an anti-CD40 antibody in the manufacture of a medicament for treating B-cell lymphoma in a subject, wherein treating comprises the steps of:

(a) measuring expression level of one or more marker genes selected from the group consisting of FITMI, 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;

(b) generating a report summarizing the expression level of one or more marker genes obtained in step (a); and

(c) administering an effective amount of the medicament to the subject if the subject is predicted to be likely to respond to the anti-CD40 antibody based on the measured expression level of the one or more marker genes provided in the report of step (b).

A ninth aspect provides use of an anti-CD40 antibody in the manufacture of a medicament for treating B-cell lymphoma in a subject, wherein treating comprises the steps of:

(a) measuring expression level of marker genes in a sample comprising B lymphoma cells obtained from said subject, wherein said marker genes are CD40 and one or more genes selected from the group consisting of FITM1, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7;

(b) generating a report summarizing the expression level of one or more marker genes obtained in step (a); and

(c) administering an effective amount of the medicament to the subject if the subject is predicted to be likely to respond to the anti-CD40 antibody based on the measured expression level of CD40 and said one or more marker genes provided in the report of step (b).

[0010] Disclosed herein are methods for assessing or aiding assessment of responsiveness of a subject having a B-cell lymphoma to treatment with an anti-CD40 antibody, comprising comparing a measured expression level of at least one marker gene in any of Tables 2-4, 6, 7 and 13 in a B-cell lymphoma sample from the subject to a reference level.

[0011] Also disclosed are methods for predicting responsiveness or monitoring treatment/responsiveness to an anti-CD40 antibody treatment in a subject having a B-cell lymphoma, comprising comparing a measured expression level of at least one marker gene in any of Tables 2-4, 6, 7 and 13 in a B-cell lymphoma sample from the subject to a reference level.

[0012] Also disclosed are methods for predicting, assessing or aiding assessment of responsiveness of a subject having a B-cell lymphoma to an anti-CD40 antibody treatment, comprising the steps of: (a) measuring 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 maker 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] Also disclosed are 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 maker 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] Also disclosed are methods for predicting, assessing or aiding assessment of responsiveness of a subject having a B-cell lymphoma to an anti-CD40 antibody treatment, comprising the steps of: (a) measuring 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) β_j is the coefficient value for each marker genes measured; (ii) p is the number of marker genes measured; (iii) x_j is transformed, normalized expression level for the sample from the subject for expression level of each marker measured; and (iv) μ_j and σ_j are means and standard deviations for each marker gene measured; wherein β_j, μ_j, and σ_j, are determined from patient samples comprising 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] Also disclosed are 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. Also disclosed are 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] Also disclosed are 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.

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 signal2noice. 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

[0038a] In the claims which follow and in the description of the invention, except where the context requires otherwise due to express language or necessary implication, the word “comprise” or variations such as “comprises” or “comprising” is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

[0039] As used herein, the terms "a subject having a B-celllymphoma" 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, ply-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotide(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping groups moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups.

Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-2'-O- allyl, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, α- anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S("thioate"), P(S)S ("dithioate"), "(O)NR 2 ("amidate"), P(O)R, P(O)OR', CO or CH 2 ("formacetal"), in which each R or R' is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (--O--) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. 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', $F(ab')_2$, 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	symb	VarW. VarB	mean	var	vscr	vscr. rank	P.Min	SCR. anti-CD40. Ab.1	IC25. anti-CD40. Ab.1	GCB. anti-CD40. Ab.1	SCR EXT. anti-CD40. Ab.1
202521_at	CTCF	0.02	10.61	0.19	-3.81	5079	0.020543	0.896744	0.758931	0.927787	0.285815
201949_x_at	CAPZB	0.04	11.78	0.33	7.92	300	0.363476	0.5627	0.9554	0.3785	0.3635
201588_at	TXNL1	0.01	13.00	0.29	-2.39	3182	2.49E-09	0.2422	0.5231	0.2540	0.1104
201070_x_at	SF3B1	0.20	9.46	0.23	-3.78	5023	0.089689	0.1715	0.1517	0.2230	0.5294
209180_at	RABGGTB	0.23	10.80	0.40	-2.89	3693	0.001233	0.9074	0.9214	0.7339	0.1495
AFFX-HSAC07/ X00351_5_at	ACTB	0.03	14.02	0.53	0.48	2039	0.144577	0.6074	0.9584	0.2415	0.4461
201891_s_at	B2M	0.13	14.67	0.22	1.98	1919	0.010118	0.2646	0.1011	0.4501	0.0392
FFX-HUMGAPDH/ M33197_5_at	GAPDH	0.59	14.78	0.04	2.95	1850	0.000944	0.7089	0.7244	0.9014	0.3096
202605_at	GUSB	0.05	10.52	0.65	-3.44	4415	6.73E-05	0.0096	0.0104	0.0053	0.0885
202854_at	HPRT1	0.03	12.92	0.30	-1.90	2773	2.64E-05	0.1297	0.2069	0.0532	0.5541
200737_at	PGK1	0.02	12.20	0.46	-2.75	3533	0.000307	0.0777	0.3535	0.0719	0.6473
201293_x_at	PPIA	0.60	14.99	0.02	3.98	1731	0.065694	0.1406	0.3579	0.1735	0.6190
201033_x_at	RPLP0	0.62	15.20	0.01	4.16	1709	0.066741	0.0667	0.1150	0.1081	0.7451
203135_at	TBP	0.06	8.29	0.19	-16.66	21417	0.001289	0.6978	0.7904	0.8630	0.2849
207332_s_at	TFRC	0.06	12.50	1.16	-0.82	2311	5.66E-06	0.1391	0.0963	0.1051	0.1710
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
229563_s_at	RPL10A	0.65	15.08	0.02	14.64	4	0.2266	0.3258	0.2266	0.6668	0.7720
203107_x_at	RPS2	0.75	15.37	0.01	14.55	5	0.2635	0.4033	0.5834	0.2635	0.6664

Probe	symb	VarW. VarB	mean	var	vscr	vscr. rank	P.Min	SCR. anti-CD40. Ab.1	IC25. anti-CD40. Ab.1	GCB. anti-CD40. Ab.1	SCR EXT. anti-CD40. Ab.1
213614_x_at	EEF1A1	0.51	16.11	0.02	14.47	6	0.2273	0.4168	0.5721	0.2273	0.6765
204892_x_at	EEF1A1	0.55	15.29	0.02	14.46	7	0.3353	0.7883	0.7755	0.5296	0.7598
212391_x_at	RPS3A	0.78	15.00	0.01	14.34	8	0.2519	0.3159	0.6319	0.2519	0.3350
211542_x_at	RPS10	0.59	15.11	0.02	14.31	9	0.2000	0.8313	0.9604	0.7117	0.7029
213583_x_at	EEF1A1	0.66	15.26	0.04	14.29	10	0.2172	0.4132	0.7604	0.2172	0.8064
200819_s_at	RPS15	0.54	15.00	0.05	13.99	11	0.3700	0.6401	0.7339	0.8220	0.7939
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
1553538_s_at	NA	0.33	15.24	0.24	13.94	15	0.5473	0.6181	0.5473	0.9966	0.9360
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
213890_x_at	RPS16	0.42	15.02	0.01	13.68	18	0.2333	0.2936	0.2333	0.3297	0.2718
212734_x_at	RPL13	0.46	14.92	0.03	13.66	19	0.2300	0.8232	0.6720	0.4503	0.7004
211983_x_at	ACTG1	0.40	14.83	0.06	13.54	20	0.4100	0.9680	0.7211	0.4205	0.7919
213801_x_at	RPSA	0.61	15.01	0.05	13.53	21	0.2661	0.4603	0.7140	0.2661	0.4003
202649_x_at	RPS19	0.33	15.03	0.03	13.44	22	0.3172	0.5861	0.5086	0.3172	0.9400
221607_x_at	ACTG1	0.41	14.73	0.06	13.38	23	0.2715	0.9680	0.6637	0.3927	0.6126
212988_x_at	ACTG1	0.45	14.53	0.06	13.31	24	0.3553	0.9075	0.6394	0.3553	0.7217
208929_x_at	RPL13	0.40	14.75	0.02	13.25	25	0.3500	0.3583	0.7912	0.9760	0.6997
200689_x_at	EEF1G	0.64	14.25	0.03	13.21	26	0.2100	0.9324	0.8163	0.8508	0.3667
211345_x_at	EEF1G	0.54	14.23	0.03	13.21	27	0.2200	0.9444	0.8022	0.7118	0.3901
211970_x_at	ACTG1	0.46	14.51	0.09	13.18	28	0.3072	0.7347	0.8427	0.7238	0.5534
211995_x_at	ACTG1	0.35	14.61	0.10	13.14	29	0.3981	0.5436	0.9959	0.9161	0.3981
200089_s_at	RPL4	0.29	15.28	0.04	13.09	30	0.2068	0.4500	0.6581	0.5132	0.5295
200024_at	RPS5	0.57	14.61	0.03	13.09	31	0.2000	0.7753	0.8060	0.5846	0.9469

Probe	symb	VarW. VarB	mean	var	vscr	vscr. rank	P.Min	SCR. anti-CD40. Ab.1	IC25. anti-CD40. Ab.1	GCB. anti-CD40. Ab.1	SCR EXT. anti-CD40. Ab.1
201550_x_at	ACTG1	0.33	14.50	0.10	13.04	32	0.3356	0.5966	0.9624	0.8531	0.4378
AFFX-r2-P1-cre-3_at	NA	0.28	15.23	0.12	13.00	33	0.4500	0.9518	0.5889	0.7244	0.8836
200003_s_at	RPL28	0.14	15.12	0.04	12.93	34	0.5687	0.9905	0.6582	0.9539	0.5687
212363_x_at	ACTG1	0.33	14.18	0.12	12.81	35	0.4219	0.6539	0.8152	0.8079	0.4254
221775_x_at	EVI1	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
214351_x_at	RPL13	0.44	14.01	0.03	12.36	42	0.2703	0.4829	0.9230	0.9173	0.4119
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
220960_x_at	RPL22	0.28	14.20	0.02	12.28	45	0.5585	0.7556	0.8571	0.7995	0.9640
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
AFFX-CreX-3_at	NA	0.27	14.50	0.19	11.83	49	0.4700	0.9276	0.5873	0.7234	0.9267
200715_x_at	RPL13A	0.26	13.87	0.12	11.70	50	0.3000	0.8556	0.3818	0.6143	0.4458
AFFX-CreX-5_at	NA	0.15	14.64	0.27	11.59	51	0.3900	0.9872	0.6546	0.5814	0.7754
222976_s_at	TPM3	0.04	14.13	0.09	11.54	52	0.3646	0.3786	0.7883	0.3646	0.5240
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

Probe	symb	VarW. VarB	mean	var	vscr	vscr. rank	P.Min	SCR. anti-CD40. Ab.1	IC25. anti-CD40. Ab.1	GCB. anti-CD40. Ab.1	SCR EXT. anti-CD40. Ab.1
221691_x_at	NPM1	0.10	15.00	0.07	11.44	55	0.5097	0.8965	0.7627	0.5097	0.7686
229353_s_at	NUCKS1	0.07	13.62	0.21	11.21	56	0.6703	0.7457	0.6703	0.7602	0.8020
1555730_a_at	CFL1	0.04	14.01	0.30	11.17	57	0.4996	0.9337	0.7560	0.4996	0.5768
200966_x_at	ALDOA	0.09	14.02	0.11	11.09	58	0.2409	0.2409	0.5526	0.4352	0.8701
224654_at	DDX21	0.06	13.50	0.13	11.07	59	0.6759	0.8439	0.8720	0.7694	0.6759
224944_at	TMPO	0.05	13.48	0.14	10.98	60	0.2455	0.3257	0.4478	0.3876	0.2455
222985_at	YWHAG	0.04	13.53	0.15	10.86	61	0.3506	0.7800	0.3506	0.9581	0.9505
1555837_s_at	POLR2B	0.07	13.18	0.16	10.85	62	0.3371	0.8399	0.3612	0.6857	0.3371
209026_x_at	TUBB	0.07	13.60	0.24	10.73	63	0.2100	0.6957	0.4642	0.7072	0.3910
238199_x_at	LOC440552	0.56	11.52	0.17	10.69	64	0.2720	0.3736	0.9156	0.2720	0.6534
217807_s_at	GLTSCR2	0.07	13.62	0.19	10.61	65	0.5757	0.8314	0.7256	0.7767	0.5757
242131_at	LOC440552	0.53	11.20	0.10	10.42	66	0.5733	0.7746	0.5733	0.7302	0.9388
222980_at	RAB10	0.12	12.27	0.13	10.40	67	0.2461	0.7382	0.9132	0.2877	0.2461
234339_s_at	GLTSCR2	0.58	11.32	0.29	10.39	68	0.6277	0.7136	0.9772	0.8445	0.6277
1554678_s_at	HNRPDL	0.04	13.21	0.22	10.39	69	0.3095	0.3381	0.3095	0.6767	0.5390
200893_at	SFRS10	0.12	13.68	0.06	10.38	70	0.3885	0.5944	0.8186	0.6001	0.3885
223105_s_at	TMEM14C	0.02	13.54	0.16	10.35	71	0.6699	0.6699	0.8055	0.8667	0.9663
224579_at	SLC38A1	0.02	13.49	0.20	10.21	72	0.2496	0.7799	0.3541	0.3506	0.2496
1558678_s_at	MALAT1	0.16	12.46	0.89	10.21	73	0.4393	0.9362	0.8914	0.4393	0.9347
223096_at	NOP5/NOP58	0.03	13.04	0.13	10.13	74	0.6162	0.6964	0.8240	0.6162	0.6685
224567_x_at	MALAT1	0.11	12.50	0.69	10.10	75	0.4566	0.9218	0.9662	0.4566	0.7071
226385_s_at	C7orf30	0.03	12.99	0.26	10.02	76	0.6285	0.6285	0.9109	0.7478	0.8336
213011_s_at	TPI1	0.04	13.56	0.18	9.96	77	0.2442	0.3471	0.6334	0.5709	0.4333
225892_at	IREB2	0.10	12.08	0.21	9.94	78	0.4034	0.8084	0.9066	0.6860	0.4034
231896_s_at	DENR	0.03	12.80	0.14	9.93	79	0.2977	0.6041	0.7701	0.2977	0.4713
201114_x_at	PSMA7	0.12	12.78	0.15	9.87	80	0.4093	0.5862	0.5983	0.8588	0.4093

Probe	symb	VarW. VarB	mean	var	vscr	vscr. rank	P.Min	SCR. anti-CD40. Ab.1	IC25. anti-CD40. Ab.1	GCB. anti-CD40. Ab.1	SCR EXT. anti-CD40. 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	SNRPD1	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-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	symb.gse	VarW. VarB	mean	var	vscr	vscr. rank	P.Min	SCR. anti-CD40	IC25. anti-CD40	GCB. anti-CD40	SCR EXT. anti-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	EVI1	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	VarW. VarB	mean	var	vscr	vscr. rank	P.Min	SCR. anti-CD40	IC25. anti-CD40	GCB. anti-CD40	SCR EXT. anti-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 complimentary 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," 3rd edition (1960) Lee G. Luna, HT (ASCP) Editor, The Blakston Division McGraw-Hill Book Company, New York; *The Armed Forces Institute of Pathology Advanced Laboratory Methods in Histology and Pathology* (1994) Ulreka V. Mikel, Editor, Armed Forces Institute of Pathology, American Registry of Pathology, Washington, D.C.). One of skill in the art will appreciate that the choice of a fixative is determined by the purpose for which the sample is to be histologically stained or otherwise analyzed. One of skill in the art will also appreciate that the length of fixation depends upon the size of the tissue sample and the fixative used. By way of example, neutral buffered formalin, Bouin's or paraformaldehyde, may be used to fix a sample.

[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, Broloid, and Tissuemay. Once the tissue sample is embedded, the sample may be sectioned by a microtome or the like (*See e.g.*, "Manual of Histological Staining Method of the Armed Forces Institute of Pathology", *supra*). By way of example for this procedure, sections may range from about three microns to about five microns in thickness. Once sectioned, the sections may be attached to slides by several standard methods. Examples of slide adhesives include, but are not limited to, silane, gelatin,

poly-L-lysine and the like. By way of example, the paraffin embedded sections may be attached to positively charged slides and/or slides coated with poly-L-lysine.

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

(b) Colloidal gold particles.

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

Current Protocols in Immunology, supra, for example. Fluorescence can be quantified using a fluorimeter.

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

[0107] Examples of enzyme-substrate combinations include, for example:

(i) Horseradish peroxidase (HRPO) with hydrogen peroxidase as a substrate, wherein the hydrogen peroxidase oxidizes a dye precursor (*e.g.*, orthophenylene diamine (OPD) or 3,3',5,5'-tetramethyl benzidine hydrochloride (TMB));

(ii) alkaline phosphatase (AP) with para-Nitrophenyl phosphate as chromogenic substrate; and

(iii) β-D-galactosidase (β-D-Gal) with a chromogenic substrate (*e.g.*, p-nitrophenyl-β-D-galactosidase) or fluorogenic substrate (*e.g.*, 4-methylumbelliferyl-β-D-galactosidase).

[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) β_j is the coefficient value for each marker genes measured; (ii) p is the number of marker genes measured; (iii) x_i is transformed, normalized expression level for the sample from the subject for expression level of each marker measured; and (iv) μ_j and σ_j are means and standard deviations for each marker gene measured; wherein β_j, μ_j and σ_j are determined from patient samples comprising B lymphoma cells from a clinical trial. In some embodiments, a value equals or greater than zero for the sensitivity index indicates that the subject is likely to respond the anti-CD40 antibody treatment, or wherein a value less than zero for the sensitivity index indicates that the subject is less likely to respond the anti-

CD40 antibody treatment. 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 rituximal plus gemzar; with rituximal 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.

[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, and these antibodies and their amino acid sequences are incorporated herein by reference. 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 $1x10^{-8}$ or no higher than $1x10^{-9}$. In some embodiments, the anti-CD40 antibody binds to CD40 and stimulates CD40 (i.e., an agonist antibody). In some embodiments, the anti-CD40 antibody increases the binding of CD40 ligand to CD40, for example, by at least 45%, by at least 50%, by at least 60%, or by at least 75%. A method of determining increases in binding of CD40 ligand to CD40 are disclosed in U.S. Pat. No. 6,838,261 (the disclosure of which is incorporated by reference herein). In some embodiments, the anti-CD40 is a humanized antibody derived from murine monoclonal antibody S2C6 described in WO 00/75348 (including antibodies provided in Tables 3 and 4 of WO 00/75348). In some embodiments, the anti-CD40 antibody comprises the heavy chain amino acid sequence shown in SEQ ID NO:1 and the light chain amino acid sequence shown in SEQ ID NO:2, for example anti-CD40 Ab.1.

D. Kits

[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 propryl silican surface chemistry are also known in the art, as disclosed at world wide web at cmt.corning.com and 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')2 fragments of a goat anti human IgG Fcγ 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 IC50, IC25 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 IC25 and IC50 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.

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

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

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

Generation and analysis of gene expression profiles

[0156] Total RNA was extracted with the *mir*Vana™ 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). 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 (www.genepattern.org). 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 $\log_2$ 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 log2-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 (μg/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
GABARAPL2	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
VARS	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, C. elegans)	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 (Drosophila)	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+ transporting, lysosomal 70kDa, V1 subunit A	-0.619955993
SLC15A2	205316_at	solute carrier family 15 (H+/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++ 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,230434_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,217788_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
GABARAPL2	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,226666_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+ 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+/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 farnesyltransferase 1	NA	NA	-0.597
MS4A7	223343_at	membrane-spanning 4-domains, subfamily A, member 7	NA	NA	-0.595
CYP39A1	244407_at	cytochrome P450, family 39, 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 (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 complex subunit-related family, member 6	NA	NA	-0.589
EYA3	1552314_a_at	eyes absent homolog 3 (Drosophila)	NA	NA	-0.587
BXDC5	218462_at	brix domain containing 5	NA	NA	-0.584
LOC401504	226635_at	NA	NA	NA	-0.583
GPR82	1553316_at	G protein-coupled receptor 82	NA	NA	-0.583
BFSP2	207399_at	beaded filament structural protein 2, phakinin	NA	NA	-0.581
SLC6A16	219820_at	solute carrier family 6, member 16	NA	NA	-0.581
NLK	238624_at	nemo-like kinase	NA	NA	-0.579
ATG3	221492_s_at	ATG3 autophagy related 3 homolog (S. cerevisiae)	NA	NA	-0.578
C19orf54	222052_at	chromosome 19 open reading frame 54	NA	NA	-0.577
PDE6D	204091_at	phosphodiesterase 6D, cGMP-specific, rod, delta	NA	NA	-0.576
235018_at	235018_at	NA	NA	NA	-0.575
KYNU	210662_at	kynureninase (L-kynurenine hydrolase)	NA	NA	-0.574
NEDD9	240019_at	neural precursor cell expressed, developmentally down-regulated 9	NA	NA	-0.574
TMEM64	225972_at	transmembrane protein 64	NA	NA	-0.574
PIGG	218652_s_at	phosphatidylinositol glycan 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++ 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-κB 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 Over-lap	Forward Primer	Reverse Primer	Probe
PRKCA	NM_002737.2	1	TGACAAAATGTAGAGGCCATTCA (SEQ ID NO:3)	CATCCGTCTCCTCTGCGATATAA (SEQ ID NO:4)	CCGTCAAACACCATTT (SEQ ID NO:5)
IGF1R	NM_000875.3	1	TTGCAAGGAAAGAAATTCAAACAC (SEQ ID NO:6)	TGCTTGAATCCATTGACTGCTT (SEQ ID NO:7)	ACAACAGCAGTAAGAAGA (SEQ ID NO:8)
BTG2	NM_006763.2	1	CAGGTCCCTGCCTTTTTAGAAG (SEQ ID NO:9)	ATCATAAAGAAGAGAAGAGAGACAAGATT AAG (SEQ ID NO:10)	AGCCTCATGGTCTCAT (SEQ ID NO:11)
LMO2	NM_005574.2	1	GGCCACAGCCCATCCA (SEQ ID NO:12)	CTTGCCCCTAAATGTTCCTTTCT (SEQ ID NO:13)	AGTAACTGACATGATTAGC (SEQ ID NO:14)
CD22	NM_001771.2	1	TTTGGAAGTGAGGCATTGCA (SEQ ID NO:15)	CCGGAGTCCCCAGAGTCAA (SEQ ID NO:16)	AGACGTACGTATCAGCG (SEQ ID NO:17)
SMN1	NM_000344.2	1	CTGGAATGTGAAGCGTTATAGAAGAT (SEQ ID NO:18)	CCTTTTTTCTTTCCCAACACTTGA (SEQ ID NO:19)	CTGGCCTCATTTCT (SEQ ID NO:20)
EPDR1	NM_017549.3	1	CAGCCTCTCTTGTCCCTGGTT (SEQ ID NO:21)	TCCCTAGCAATGGACAAACTCA (SEQ ID NO:22)	CCTTATGTGTTGAATGTGG (SEQ ID NO:23)
CD40	NM_001250.4	1	GGGATCCTGTTTGCCATCCT (SEQ ID NO:24)	GCTTCTTGGCCACCTTTTTG (SEQ ID NO:25)	TTGGTGCTGGTCTTT (SEQ ID NO:26)
IFITM1	NM_003641.3	1	GGCTTCATAGCATTCGCCTACT (SEQ ID NO:27)	TCACGTCGCCAACCATCTT (SEQ ID NO:28)	CGTGAAGTCTAGGGACAG (SEQ ID NO:29)
VNN2	NM_004665.2	1	GACTTGTATGTATGGGAGTGAGGAGT T (SEQ ID NO:30)	TCTCTTCAAGGGCACAGCTATG (SEQ ID NO:31)	CAGGGCCATTGCAA (SEQ ID NO:32)
PRPSAP 2	NM_002767.2	1	GCCAAACTGGAAACATAAGAGTGA (SEQ ID NO:33)	GCATGACGGTTCCTGTGAAA (SEQ ID NO:34)	TGCTCGGTGGGATGG (SEQ ID NO:35)
PRKCA	NM_002737.2	1	CGGAGGTTGAGGTTTTTCCTT (SEQ ID NO:36)	GACGGTTGAATGGCCTCTACA (SEQ ID NO:37)	TGTATAAGCACCTACTGACA AA (SEQ ID NO:38)
IGF1R	NM_000875.3	1	AGGACTTCTTCATGGGTCTTACAGTT (SEQ ID NO:39)	AAGTGACATTAAAGACGATGTGTATGC (SEQ ID NO:40)	TGTTAGACCATGAAACATT (SEQ ID NO:41)
BTG2	NM_006763.2	1	CAGGCTGTGTTCTTGCATCTTG (SEQ ID NO:42)	GACCATGAGGCTGCTTCTAAAAA (SEQ ID NO:43)	CTGCAAACAGGTCCCT (SEQ ID NO:44)
LMO2	NM_005574.2	1	TTGGACCCAAGGGAAAACTG (SEQ ID NO:45)	GGTTAAAAGTTGTGGTTTCCATTCTC (SEQ ID NO:46)	TGGAGACGCATTTCG (SEQ ID NO:47)
CD22	NM_001771.2	1	GACATCCCCACTCACGAATATTATG (SEQ ID NO:48)	CTGTCCTTTTCTGGGCTTTCC (SEQ ID NO:49)	CCAGTTTCTGCCTCTGA (SEQ ID NO:50)

Gene Locus	GenBank Accession No.	Probe Over-lap	Forward Primer	Reverse Primer	Probe
SMN1	NM_000344.2	1	GGCATAGAGCAGCACTAAATGACA (SEQ ID NO:51)	TTCTATAACGCTTCACATTCCAGATC (SEQ ID NO:52)	CACTAAAGAAACGATCAGAC (SEQ ID NO:53)
EPDR1	NM_017549.3	0	CGCACTTTGGCCTTCCTAGA (SEQ ID NO:54)	TGGAAGGAGATGCAGAAGTCAGA (SEQ ID NO:55)	CACTGCTTCATAACCTC (SEQ ID NO:56)
CD40	NM_001250.4	1	CCTGCCCAGTCGGCTTCT (SEQ ID NO:57)	GTCCAAGGGTGACATTTTTCG (SEQ ID NO:58)	CTCCAATGTGTCATCTG (SEQ ID NO:59)
IFITM1	NM_003641.3	1	GGGTTACTAGTAGCCGCCCATA (SEQ ID NO:60)	GCAGGGCCAGCATTGC (SEQ ID NO:61)	CAACCTTTGCACTCCAC (SEQ ID NO:62)
VNN2	NM_004665.2	1	TGTCCATTTTTTTGGCTACTCTGA (SEQ ID NO:63)	CCCAAACACCCAGGCTCTT (SEQ ID NO:64)	CAGTGTGGAACAATG (SEQ ID NO:65)
PRPSAP 2	NM_002767.2	0	GCTCCAGTGCCCCAAGATT (SEQ ID NO:66)	CGACGGATCGCCTCTGAA (SEQ ID NO:67)	AAACTGTGGATATCAGCATG A (SEQ ID NO:68)
PRKCA	NM_002737.2	0	TGGGCAACTCAGAAATACTTCGA (SEQ ID NO:69)	ACGTCAATAGGCACGTTTGCT (SEQ ID NO:70)	CTCCCAAGATATAAGAGGC (SEQ ID NO:71)
IGF1R	NM_000875.3	0	GTCCACCCTCTCCCCTTTCT (SEQ ID NO:72)	CACGCACTCTAGTACAAAGCATAAGA (SEQ ID NO:73)	CTCACTCCAAGAAAC (SEQ ID NO:74)
BTG2	NM_006763.2	0	CCCAAACCGAATCACCTTAAGA (SEQ ID NO:75)	CAGGAGGGTGGCCATCCT (SEQ ID NO:76)	ACAGGGCTAGGGCAT (SEQ ID NO:77)
LMO2	NM_005574.2	0	TCTCCATGGCATCTTCGTCTT (SEQ ID NO:78)	ATCCCTTACCCCACCCTCAA (SEQ ID NO:79)	ACTCTTAGGCACTTTGG (SEQ ID NO:80)
CD22	NM_001771.2	0	CGGCCTCAGGCACAAGAA (SEQ ID NO:81)	GCAGCCCATCCAGTGTCAAT (SEQ ID NO:82)	ATGTGGACTATGTGATCCT (SEQ ID NO:83)
SMN1	NM_000344.2	0	CATGGTACATGAGTGGCTATCATACT G (SEQ ID NO:84)	GTGAGCACCTTCCTTCTTTTTGA (SEQ ID NO:85)	CTATTATATGGGTTTCAGAC AAA (SEQ ID NO:86)
EPDR1	NM_017549.3	0	GACTATTGTCTCCTAAACCCAGGACT A (SEQ ID NO:87)	CCCAGTGCATTTAATGACCAAA (SEQ ID NO:88)	AGTTCCCTCGTACTGTC (SEQ ID NO:89)
CD40	NM_001250.4	1	ATCAATTTTCCCGACGATCTTC (SEQ ID NO:90)	CGGTTGGCATCCATGTAAAGT (SEQ ID NO:91)	TGGCTCCAACACTG (SEQ ID NO:92)
IFITM1	NM_003641.3	0	AGGTCCACCGTGATCAACATC (SEQ ID NO:93)	CAGGGACCAGACGACATGGT (SEQ ID NO:94)	ACAGCGAGACCTCCGT (SEQ ID NO:95)
VNN2	NM_004665.2	0	CAACTTGTGGACGGCCAGTA (SEQ ID NO:96)	GTGCCACTGAGGGAGAACATTT (SEQ ID NO:97)	AAACTGCTTCTACAAGATT (SEQ ID NO:98)
PRPSAP 2	NM_002767.2	0	CAGCAGAGACCCTGAAGGAAA (SEQ ID NO:99)	CAAGCCATGAGTTGCCATCA (SEQ ID NO:100)	AGGTGCATATAAGATCTT (SEQ ID NO:101)

Gene Locus	GenBank Accession No.	Probe Over-lap	Forward Primer	Reverse Primer	Probe
BCL6	NM_001706.2	1	CCCATTCTGCGTCATGCTT (SEQ ID NO:102)	AATGCAGTTTAGACACAGCCAAAC (SEQ ID NO:103)	TGTTATAACTACTCCGGAGA CAG(SEQ ID NO:104)
LRRC8A	NM_019594.2	1	AGTTCAGCCCCAGATGGAAGGT (SEQ ID NO:105)	GCGGCATCGGCTAAATAAGGA (SEQ ID NO:106)	TTCAGGGAAAGGTGGGC (SEQ ID NO:107)
BCL6	NM_001706.2	1	CACAGGGACTTGAAGTTGTTACTAAC TAA (SEQ ID NO:108)	TGACGCAGAATGGGATGAGA (SEQ ID NO:109)	CTCTCTTTGGGAATGTT (SEQ ID NO:110)
LRRC8A	NM_019594.2	0	CAAAGCAGCCAGACGTTGAAC (SEQ ID NO:111)	CACACCAGATCCGGAAGACA (SEQ ID NO:112)	TTTCCCTGGGCGCAGG (SEQ ID NO:113)
RGS13	NM_144766.1	0	GGGATTCCTACCCCAGATTTCTA (SEQ ID NO:114)	CAGAAACTGTTGTTGGACTGCATAG (SEQ ID NO:115)	AGTCAGAAATGTACCAAAAA (SEQ ID NO:116)
YIPF3	NM_015388.2	1	TGAGCTGTAGCTGCGTAAGTACCT (SEQ ID NO:117)	GGCCTTGTGCCTTTCAGAAG (SEQ ID NO:118)	CTTGATGCCCTGTCGGC (SEQ ID NO:119)
YIPF3	NM_015388.2	1	TGGCTGCCCTACACATGCT (SEQ ID NO:120)	CAGGATCCCCCTCTACCACTTTG (SEQ ID NO:121)	CCTGCTCTATCTGCATTT (SEQ ID NO:122)
YIPF3	NM_015388.2	0	GAGGCTCAGCTGTGATTGACAT (SEQ ID NO:123)	CACCCATATCCCTCGAAGCTAGAG (SEQ ID NO:124)	AGAACATGGATGATACCTC (SEQ ID NO:125)
RGS13	NM_144766.1	0	TCCAGCCACAGTCCCCTAGA (SEQ ID NO:126)	TCCTGAATGTTCCTGATGATAGTCTCT (SEQ ID NO:127)	AGATTAACATTGACAGTTCG ACA(SEQ ID NO:128)
EPDR1	NM_017549.3	0	CGAGAGGAAGGCGCTGATC (SEQ ID NO:129)	ACATCACTCCATCCTTATACAGCAAA (SEQ ID NO:130)	CCTGCAAGAGATTATTT (SEQ ID NO:131)
EPDR1	NM_017549.3	0	GGATCCTCTTGACATTCCTCAAA (SEQ ID NO:132)	GGCCCCCCGATGGA (SEQ ID NO:133)	CTCCACCTTTGAAGACC (SEQ ID NO:134)
EPDR1	NM_017549.3	0	CGAGGGTGTGGCCATATGA (SEQ ID NO:135)	GAACAGGCATTAGAAATACCCAAAG (SEQ ID NO:136)	TGACTAGATGGCTAATATG (SEQ ID NO:137)
UAP1	NM_003115.4	0	CTACTGCAAGGCATGCTTTGAT (SEQ ID NO:138)	TGGCCCCCTGCATTGA (SEQ ID NO:139)	TCCCTTCATCATTGCTG (SEQ ID NO:140)
CD79B	NM_000626.2	0	GCCGGTGCAGTTACACGTT (SEQ ID NO:141)	CCCCAAACCCGTGACAAC (SEQ ID NO:142)	CCTCCAAGGAGCCTC (SEQ ID NO:143)
CLPTM1	NM_001294.1	1	CAAGGCCCTCAACACATTCA (SEQ ID NO:144)	GGTACATAACGGGCATCTTGATG (SEQ ID NO:145)	ACCTGTTCGCCTTTG (SEQ ID NO:146)
UAP1	NM_003115.4	1	CCTATGCTGGAGAAGGATTAGAAAGT (SEQ ID NO:147)	CGATGATTAGAGGTGCATGGAA (SEQ ID NO:148)	ATGTGGCAGATAAAG (SEQ ID NO:149)
CD79B	NM_000626.2	0	TCTCGCCACCCTCACCAT (SEQ ID NO:150)	GCTGACAGAAGTAGATGCCATTGT (SEQ ID NO:151)	CAAGGCATCCGGTTTG (SEQ ID NO:152)

Gene Locus	GenBank Accession No.	Probe Over-lap	Forward Primer	Reverse Primer	Probe
CLPTM1	NM_001294.1	0	AAGTCGCCCTGGAACTTCCT (SEQ ID NO:153)	CACCGAGTCCTGCTCCTCAT (SEQ ID NO:154)	ATGAGTTGTACGAGCAGTC (SEQ ID NO:155)
UAP1	NM_003115.4	1	CATGAGCTGGTGAAAAATGGTATTT (SEQ ID NO:156)	AAAGCTATTCCTATCGTGGCAAA (SEQ ID NO:157)	AACCAGATACCAAGTTTT (SEQ ID NO:158)
CD79B	NM_000626.2	1	TCCCCAGCTCTTGCCAAAG (SEQ ID NO:159)	CAGAGAACTCCCTCCAAGTTGCT (SEQ ID NO:160)	CTGGAGTAGAAGGACAACAG (SEQ ID NO:161)
CLPTM1	NM_001294.1	0	GGCAGGCCAGGGTTTGT (SEQ ID NO:162)	CGAGATGGCTGGAAACACAGA (SEQ ID NO:163)	AGGCGCTGTCTGTC (SEQ ID NO:164)
CTSC	NM_001814.3	1	GACTCAGCCTCTGGGATGGA (SEQ ID NO:165)	GGATCCGGAAGTAGCCATTCT (SEQ ID NO:166)	TGGATTGTTAAAAACAGCTG G (SEQ ID NO:167)
CTSC	NM_001814.3	0	AGGCGGCTTCCCATACCT (SEQ ID NO:168)	CTTCTTCCACCAGCCCAAAA (SEQ ID NO:169)	ATTGCAGGAAAGTACGCC (SEQ ID NO:170)
CTSC	NM_001814.3	0	CCCAAACCTGCACCACTGA (SEQ ID NO:171)	CAAGATGTTGGCAAATGCAAA (SEQ ID NO:172)	CTGAAATACAGCAAAAGA (SEQ ID NO:173)
CD44	NM_000610.3	0	CCTTTGTGGCATTTATTCATCAGT (SEQ ID NO:174)	GCTTCTATGACAAGCAGCCTTTG (SEQ ID NO:175)	AGGGTGTCCGATTGG (SEQ ID NO:176)
PUS7	NM_019042.3	0	CTCTGTAGCACAGGCTGGATTG (SEQ ID NO:177)	AGGCTGCAGTGCAAGATTGA (SEQ ID NO:178)	AGTGCAATCCTGCAATT (SEQ ID NO:179)
CD44	NM_000610.3	0	CCACTTGGAGGCCTTTCATC (SEQ ID NO:180)	AGGTTGGCGATCAGGAATACA (SEQ ID NO:181)	TCGGGTGTGCTATGGA (SEQ ID NO:182)
PUS7	NM_019042.3	0	CCTTGCCTGGTTTCGATGTT (SEQ ID NO:183)	GAGCATTTCCCTGTAGGCTTCTT (SEQ ID NO:184)	CCCAAAGCATAAAATT (SEQ ID NO:185)
CD44	NM_000610.3	0	CAACCGTTGGAAACATAACCATT (SEQ ID NO:186)	AACAATCAGTAGCACATTGCATCTG (SEQ ID NO:187)	AGGGAGCTGGGACACT (SEQ ID NO:188)
PUS7	NM_019042.3	0	TGGACTCACTGAGGCTGACGTA (SEQ ID NO:189)	GATTCCCGAGAACCCTTGATG (SEQ ID NO:190)	TCACCAAGTTTGTGAGTTC (SEQ ID NO:191)
RPL22	NM_000983.3	1	GCTGCCAATTTTGAGCAGTTT (SEQ ID NO:192)	GTTCCCAGCTTTTTCCGTTCA (SEQ ID NO:193)	TGCAAGAAAGGATCAAA (SEQ ID NO:194)
LOC728179	XR_015348.1	1	TCTTGCCTGCCCTGTTG (SEQ ID NO:195)	TGCCTTCCCCTTAATAATGCA (SEQ ID NO:196)	AAAATGCGGGTCCCTT (SEQ ID NO:197)
SERBP1	NM_001018067.1	1	CTCCCGCTACACAGAAGTAACAAA (SEQ ID NO:198)	AAAACATCCCTGCTACCAATACATT (SEQ ID NO:199)	ATGGTAGTCAGTTTTGTATT TAG (SEQ ID NO:200)
RPL9	NM_000661.4	1	TCCGTTACAAGATGAGGTCTGTGT (SEQ ID NO:201)	CATTCTCCTGGATAACAACGTTGA (SEQ ID NO:202)	TGCTCACTTCCCC (SEQ ID NO:203)

Gene Locus	GenBank Accession No.	Probe Over-lap	Forward Primer	Reverse Primer	Probe
CFL1	NM_005507.2	1	TCCATCCCTTGACGGTTCTG (SEQ ID NO:204)	AGCCCAAGAGGAATCAAAAGATC (SEQ ID NO:205)	CCTTCCCAAACTGCTTT (SEQ ID NO:206)
RPL13	NM_000977.2	1	GAGTCATCACTGAGGAAGAGAAGAAT T (SEQ ID NO:207)	TGGCACGGGCCATACG (SEQ ID NO:208)	CAAAGCCTTCGCTAGTC (SEQ ID NO:209)
FLJ16025	NM_198505.1	1	CCTACACCCCTTATCCCCATACT (SEQ ID NO:210)	CCAGGGCTATTGGTTGAATGA (SEQ ID NO:211)	TTATTATCGAAACCATCAGC C (SEQ ID NO:212)
RPS10	NM_001014.3	1	CGACCTGCGAGACTCACAAG (SEQ ID NO:213)	GGCACAGCACTCCGTCTGT (SEQ ID NO:214)	AAGCTGACAGAGATACC (SEQ ID NO:215)
NPM1	NM_002520.5	1	TCTGGCTGTCCTTTTTATAATGCA (SEQ ID NO:216)	CTTGGCAATAGAACCTGGACAAC (SEQ ID NO:217)	AGTGAGAACTTTCCC (SEQ ID NO:218)
CCDC72	NM_015933.3	1	GCAAGAAGAAGCCACTGAAACA (SEQ ID NO:219)	GAAAGCCTTATCTTCCTCGTCCAT (SEQ ID NO:220)	CCCAAGAAGCAGGCCA (SEQ ID NO:221)
RPS19	NM_001022.3	1	GGCTGAAAATGGTGGAAAAGG (SEQ ID NO:222)	CTTTGTCCCTGAGGTGTCAGTTT (SEQ ID NO:223)	CCAAGATGGCGGCCG (SEQ ID NO:224)
RPS16	NM_001020.4	1	TGTGGATGAGGCTTCCAAGAA (SEQ ID NO:225)	CAGCAGGGTCCGGTCATACT (SEQ ID NO:226)	AGATCAAAGACATCCTCATC (SEQ ID NO:227)
EEF1G	NM_001404.4	1	GGCAGGTGGACTACGAGTCATAC (SEQ ID NO:228)	GTCTCCTCGCTGCCAGGAT (SEQ ID NO:229)	CATGGCGGAAACTG (SEQ ID NO:230)
RPS5	NM_001009.3	1	CCGGAACATTAAGACCATTGC (SEQ ID NO:231)	CCCTTGGCAGCATTGATGA (SEQ ID NO:232)	AGTGCCTGGCAGATG (SEQ ID NO:233)
EEF1A1	NM_001402.5	1	CTGCCACCCCACTCTTAATCA (SEQ ID NO:234)	GGCCAATTGAAACAAACAGTTCT (SEQ ID NO:235)	TGGTGGAAGAACGGTC (SEQ ID NO:236)
RPL28	NM_000991.3	1	GGAAGCCTGCCACCTCCTAT (SEQ ID NO:237)	TGGCGCGAGCATTCTTG (SEQ ID NO:238)	TGCGGACCACCATC (SEQ ID NO:239)
ACTG1	NM_001614.2	1	TGTCCTTGAAGCTTGTATCTGATATC A(SEQ ID NO:240)	TTCAATACAAGGTCAAAATCAGCAA (SEQ ID NO:241)	CACTGGATTGTAGAACTT (SEQ ID NO:242)
BTF3	NM_001037637.1	1	AGCCTCAGATGAAAGAAACAATCA (SEQ ID NO:243)	CACTTGTGCCTGCAGTTTGG (SEQ ID NO:244)	AACCAGGAAAAACTC (SEQ ID NO:245)
TMSB4X	NM_021109.2	1	AAGCAGGCGAATCGTAATGAG (SEQ ID NO:246)	TGCTTGTGGAATGTACAGTGCAT (SEQ ID NO:247)	CGTGCGCCGCCAA (SEQ ID NO:248)
TPM3	NM_153649.3	1	CCCTTTCTGGGTTTGAAGCT (SEQ ID NO:249)	CTGACTGATACAAAGCACAATTGAGA (SEQ ID NO:250)	CTGTCTCTAGAAGTGCC (SEQ ID NO:251)
USMG5	NM_032747.2	1	GCTGTGAAAGCAACATAAATGGAT (SEQ ID NO:252)	GGCATGGGAACTTAACAGATGAG (SEQ ID NO:253)	TTAAACTGTCTACGGTTCTT (SEQ ID NO:254)

Gene Locus	GenBank Accession No.	Probe Over-lap	Forward Primer	Reverse Primer	Probe
EIF1	NM_005801.3	1	CGCTATCCAGAACCTCCACTCT (SEQ ID NO:255)	CAGGTCATCACCCTTACTTGCA (SEQ ID NO:256)	TCGACCCCCTTTGCTG (SEQ ID NO:257)

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 at www-stat.stanford.edu/~hastie/Papers/glmnet.pdf. X^2 tests were used to test for associations among categorical variables.

Normalization, Transformation and Imputation

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

Definitions

Assay Data

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

Model Parameters

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

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

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

Formulas

Reference Set Model Parameters

Intermediate values

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

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

Model parameters

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

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

Transformed, Normalized Assay Values

Intermediate values

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

Transformed, normalized, imputed assay values

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

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

The completed $N_\ell \times p$ matrix of values, $\begin{bmatrix} \mathbf{x}_1^{(Obs)} & \cdots & \mathbf{x}_p^{(Obs)} \\ \mathbf{x}_1^{(ND)} & \cdots & \mathbf{x}_p^{(ND)} \end{bmatrix}$, 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

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

Model Parameters

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

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

Formulas

Reference Set Model Parameters

Probe Means and Standard Deviations

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

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

Index and Classifier

Sensitivity Index

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

Sensitivity Class

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

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

<table>
<tr><td colspan="2">Diagnostic Assay</td><td></td><td colspan="2">Clinical Database</td></tr>
<tr><td>Archival FFPE specimens</td><td>29</td><td rowspan="4">Analysis sample size (both qRT-PCR and SPD available)</td><td></td><td></td></tr>
<tr><td># of patients (3 with multiple specimens)</td><td>24</td><td></td><td></td></tr>
<tr><td>Specimens qRT-PCR Reported</td><td>27</td><td></td><td></td></tr>
<tr><td>Usable qRT-PCR results (1 insufficient)</td><td>26</td><td>46</td><td>Patients in clinical database</td></tr>
<tr><td>qRT-PCR for unique patients (2 patient specimen pairs averaged together)</td><td>24</td><td>21</td><td>39</td><td>SPD Change from Baseline Reported</td></tr>
</table>

[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 95th percentile confidence intervals, based upon 5,000 replicates sampled with replacement from the DLBCL patient sample, N=21. Narrower ranges will become available as the sample size increases. Since no model-building or checking was required to produce these results, they comprise a robust trend, which confirms that these qRT-PCR probe measurements are associated, overall, with reduction in tumor SPD in patients treated with anti-CD40 Ab.1.

Table 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 μ_j and σ_j values obtained are as shown in Table 15.

Table 15: μ_j and σ_j ranges based on data from Clinical Trail 001

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

μ_j	RGS13	EPDR1	CD79B	UAP1	CTSC	CD44	PUS7

lower	-5.14	-5.19	-5.10	-5.26	-5.04	-4.97	-5.24
upper	-5.00	-5.12	-5.04	-5.18	-4.95	-4.87	-5.16

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

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

Clinical Trial 002 Results

[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 ≥ 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	?

[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.

CLAIMS

1. A method for predicting 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 FITM1, 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).

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

(a) measuring expression level of marker genes in a sample comprising B lymphoma cells obtained from said subject, wherein said marker genes are CD40 and one or more genes selected from the group consisting of FITM1, 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 CD40 and said one or more marker genes from step (a).

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

4. The method of any one of claims 1 to 3, wherein the anti-CD40 antibody treatment is a treatment with an agonist anti-CD40 antibody, and wherein an increased expression of one or more of FITM1, 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.

5. The method of claim 4, 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.

6. The method of claim 5, 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.

7. The method of claim 2 or claim 3, wherein the anti-CD40 antibody treatment is a treatment with an agonist anti-CD40 antibody, and 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.

8. The method of claim 7, 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.

9. The method of claim 8, 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.

10. The method of any one of claims 4 to 9, wherein the agonist anti-CD40 antibody stimulates CD40 and enhances the interaction between CD40 and CD40 ligand.

11. The method of claim 10, 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.

12. The method of any one of claims 4 to 9, wherein the agonist anti-CD40 antibody stimulates CD40 and does not enhance or inhibit the interaction between CD40 and CD40 ligand.

13. The method of any one of claims 1 to 12, further comprising measuring expression level of BCL6, wherein the a higher expression level of BCL6 as compared to a reference level and indicates that the subject is likely to respond to the anti-CD40 antibody treatment.

14. The method of claim 13, 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.

15. The method of any one of claims 1 to 14, further comprising administering an effective amount of an anti-CD40

antibody to the subject if the subject is predicted to be likely to respond to the anti-CD40 treatment based on the measured expression levels of said marker genes.

16. A method of treating a subject having B-cell lymphoma comprising the steps of:

(a) measuring expression level of one or more marker genes selected from the group consisting of FITMI, 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;

(b) generating a report summarizing the expression level of one or more marker genes obtained in step (a); and

(c) administering an effective amount of an anti-CD40 antibody to the subject if the subject is predicted to be likely to respond to the anti-CD40 antibody treatment based on the measured expression level of the one or more marker genes provided in the report of step (b).

17. A method of treating a subject having B-cell lymphoma comprising the steps of:

(a) measuring expression level of marker genes in a sample comprising B lymphoma cells obtained from said subject, wherein said marker genes are CD40 and one or more genes selected from the group consisting of FITM1, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7;

(b) generating a report summarizing the expression level of one or more marker genes obtained in step (a); and

(c) administering an effective amount of an anti-CD40 antibody to the subject if the subject is predicted to be likely to respond to the anti-CD40 antibody treatment based on

the measured expression level of CD40 and said one or more marker genes provided in the report of step (b).

18. The method of claim 16 or claim 17, wherein the expression level is normalized.

19. The method of any one of claims 16 to 18, wherein the report includes a recommendation for an anti-CD40 antibody treatment for the subject.

20. The method of any one of claims 16 to 19, wherein the anti-CD40 antibody treatment is a treatment with an agonist anti-CD40 antibody, and wherein an increased expression of one or more of FITM1, 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.

21. The method of claim 20, 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.

22. The method of claim 21, wherein the samples from subjects for reference level determination comprise the same type of B lymphoma cells as the sample from the subject whose personalized genomics profile is prepared.

23. The method of any one of claims 16 to 19, wherein the anti-CD40 antibody treatment is a treatment with an agonist anti-CD40 antibody, 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 the agonist anti-CD40 antibody treatment.

24. The method of claim 23, 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.

25. The method of claim 24, wherein the samples from subjects for reference level determination comprise the same type of B lymphoma cells as the sample from the subject whose personalized genomics profile is prepared.

26. The method of any one of claims 16 to 25, wherein the agonist anti-CD40 antibody stimulates CD40 and enhances the interaction between CD40 and CD40 ligand.

27. The method of claim 26, 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.

28. The method of any one of claims 16 to 25, wherein the agonist anti-CD40 antibody stimulates CD40 and does not enhance or inhibits the interaction between CD40 and CD40 ligand.

29. The method of any one of claims 1, 3 to 12, or 16 to 28, wherein the expression level 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 are measured.

30. The method of any one of claims 2, 7 to 12, or 16 to 28, wherein 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, at least fourteen, or fifteen marker genes are measured.

31. The method of claim 19 or claim 20, wherein the expression level of FITM1, RGS13, CD79B, CD22, BTG2, CD44, EPDR1, and UAP1 are measured.

32. The method of any one of claims 16 to 31, wherein the B cell lymphoma is diffuse large B-cell lymphoma (DLBCL).

33. The method of any one of claims 16 to 31, wherein the B cell lymphoma is non-Hodgkin's lymphoma.

34. The method of claim 33, wherein the non-Hodgkin's lymphoma is follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, or small lymphocytic lymphoma.

35. The method of any one of claims 16 to 34, wherein the sample comprising the B lymphoma cells is formalin fixed paraffin embedded biopsy sample.

36. The method of any one of claims 16 to 35, wherein the expression level of said marker genes is measured by the level of an RNA transcript of said marker genes.

37. The method of claim 36, wherein the RNA transcript is measured by qRT-PCR.

38. The method of any one of claims 16 to 35, wherein the expression level of said marker genes is measured by the level of the protein expression of said marker genes.

39. A method for predicting 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 FITM1, 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) β_j is the coefficient value for each marker genes measured; (ii) p is the number of marker genes measured; (iii) x_j is transformed, normalized expression level for the sample from the subject for expression level of each marker measured; and (iv) μ_j and σ_j are means and standard deviations for each marker gene measured; wherein β_j, μ_j and σ_j are determined from patient samples comprising B lymphoma cells from a clinical trial; and

wherein 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.

40. The method of claim 39, wherein 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.

41. The method of claim 39 or claim 40, wherein the expression level of FITM1, RGS 13, CD79B, CD22, BTG2, CD44, EPDR1, and UAP1 are measured and used for the sensitivity index calculation.

42. The method of any one of claims 39 to 41, wherein β_j, μ_j and σ_j are determined from patient samples have the same type of B lymphoma cells as the sample from subject whose responsiveness to the anti-CD40 treatment is predicted.

43. The method of any one of claims 39 to 42, further comprising administering an effective amount of an anti-CD40 antibody to the subject if the subject is predicted to be likely to respond to the anti-CD40 treatment based on the measured expression levels of the two or more marker genes.

44. A kit when used in the method of any one of claims 1, 3 to 6, 10 to 16, 18 to 29, or 31 to 43, the kit comprising reagents for measuring expression level of at least one marker

gene selected from the group consisting of FITM1, CD79B, IGFIR, CD44, CTSC, EPDR1, PUS7, RGS13, VNN2, LM02, CD22, BTG2, and UAP1 in a sample comprising B lymphoma cells from a subject.

45. A kit when used in the method of any one of claims 2 to 14, 17 to 28, or 30 to 43, the kit comprising reagents for measuring expression level of at least two marker genes, wherein the marker genes are CD40 and one or more marker genes selected from the group consisting of FITM1, CD79B, IGFIR, CD44, CTSC, EPDR1, PUS7, RGS13, VNN2, LM02, CD22, BTG2, and UAP1 in a sample comprising B lymphoma cells from a subject.

46. The kit of claim 44 or claim 45, wherein the reagents comprise at least a pair of primers and a probe for detecting expression level of each marker gene by qRT-PCR.

47. The kit of claim 46, wherein said pair of primers and probe is 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:l14, 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.

48. The kit of any one of claims 44 to 47, further comprising reagents for measuring expression level of BCL6 in the sample comprising B lymphoma cells from the subject.

49. The kit of claim 48, wherein the reagents comprise at least a pair of primers and a probe for detecting the expression level of BCL6 by qRT-PCR.

50. The kit of claim 49, wherein said pair primer and probe is SEQ ID NOS:102, 103, and 104, or SEQ ID NOS:108, 109, and 110.

51. Use of an anti-CD40 antibody in the manufacture of a medicament for treating a subject having B-cell lymphoma, wherein treating comprises the steps of:

(a) measuring expression level of one or more marker genes selected from the group consisting of FITMI, 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;

(b) generating a report summarizing the expression level of one or more marker genes obtained in step (a); and

(c) administering an effective amount of the medicament to the subject if the subject is predicted to be likely to respond to the anti-CD40 antibody based on the measured

expression level of the one or more marker genes provided in the report of step (b).

52. Use of an anti-CD40 antibody in the manufacture of a medicament for treating a subject having B-cell lymphoma, wherein treating comprises the steps of:

(a) measuring expression level of marker genes in a sample comprising B lymphoma cells obtained from said subject, wherein said marker genes are CD40 and one or more genes selected from the group consisting of FITM1, RGS13, VNN2, LMO2, CD79B, CD22, BTG2, IGF1R, CD44, CTSC, EPDR1, UAP1, and PUS7;

(b) generating a report summarizing the expression level of one or more marker genes obtained in step (a); and

(c) administering an effective amount of the medicament to the subject if the subject is predicted to be likely to respond to the anti-CD40 antibody based on the measured expression level of CD40 and said one or more marker genes provided in the report of step (b).

53. The method of any one of claims 1, 2, 16, 17 or 39, the kit of claim 44 or claim 45, or the use of claim 51 or claim 52, substantially as hereinbefore described with reference to the examples and figures.

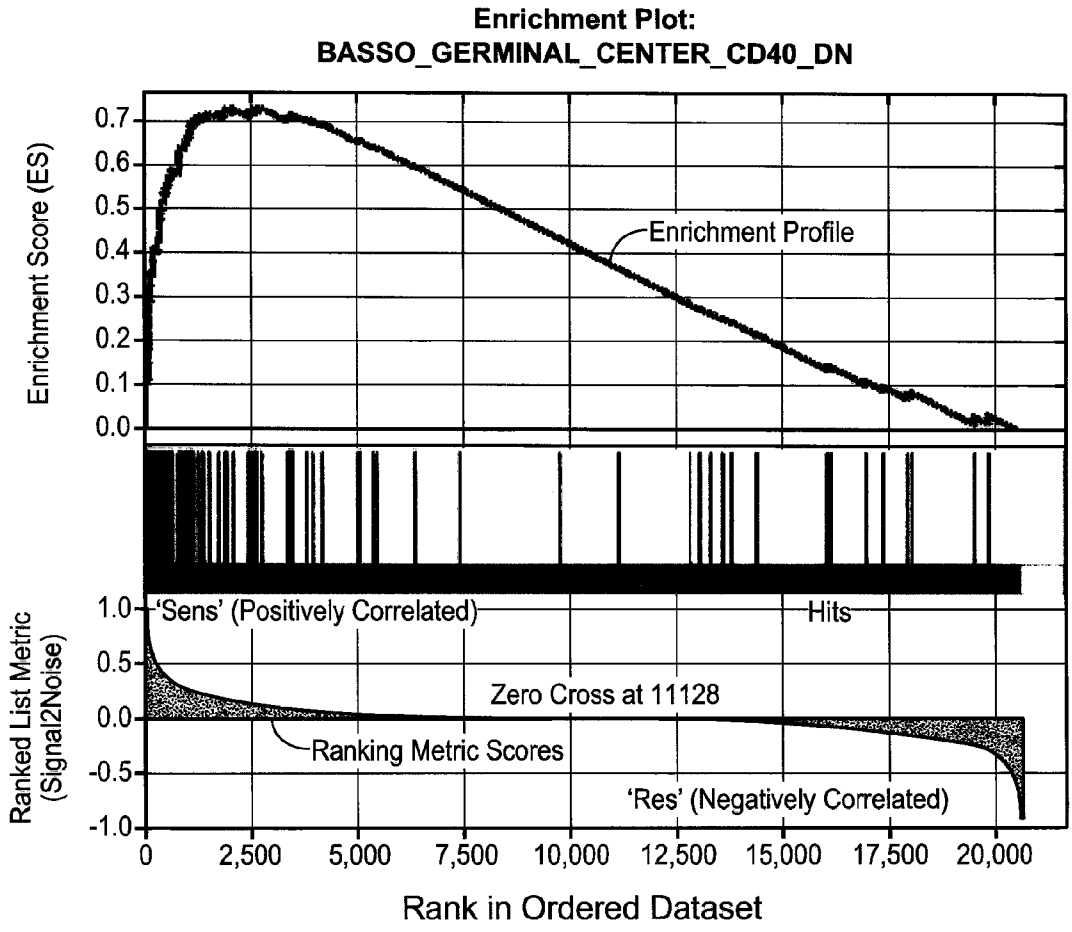
Enrichment Plot:
BASSO_GERMINAL_CENTER_CD40_DN
Enrichment Score (ES)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Enrichment Profile
'Sens' (Positively Correlated)
Hits
Ranked List Metric (Signal2Noise)
1.0
0.5
0.0
-0.5
-1.0
Zero Cross at 11128
Ranking Metric Scores
'Res' (Negatively Correlated)
0
2,500
5,000
7,500
10,000
12,500
15,000
17,500
20,000
Rank in Ordered Dataset

FIG. 1

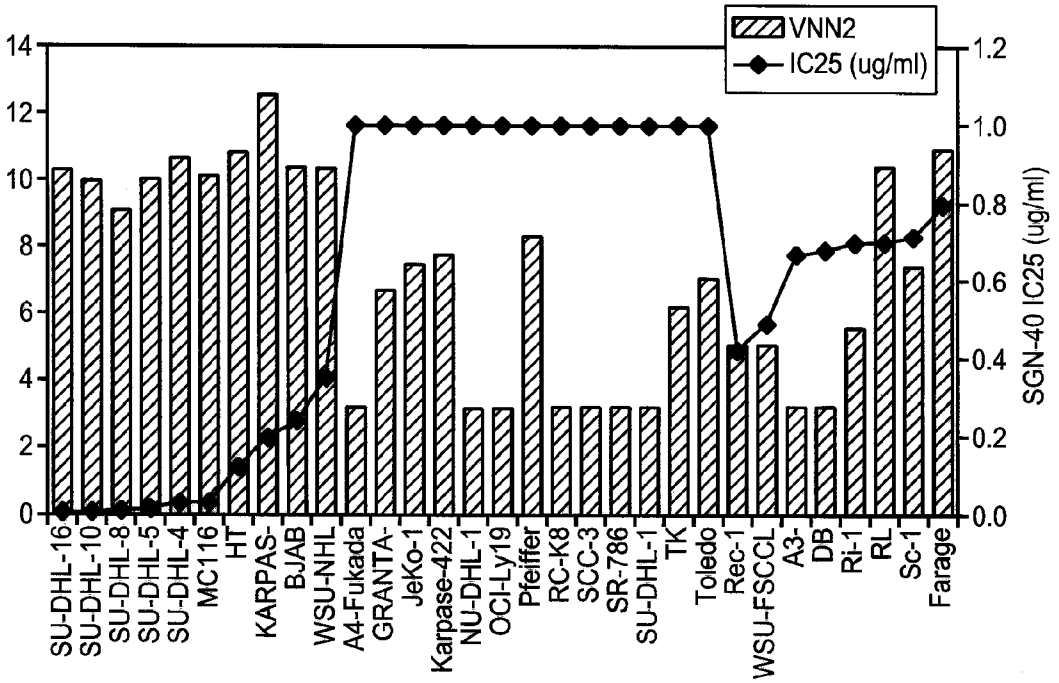

FIG. 2

NHL Cell Lines

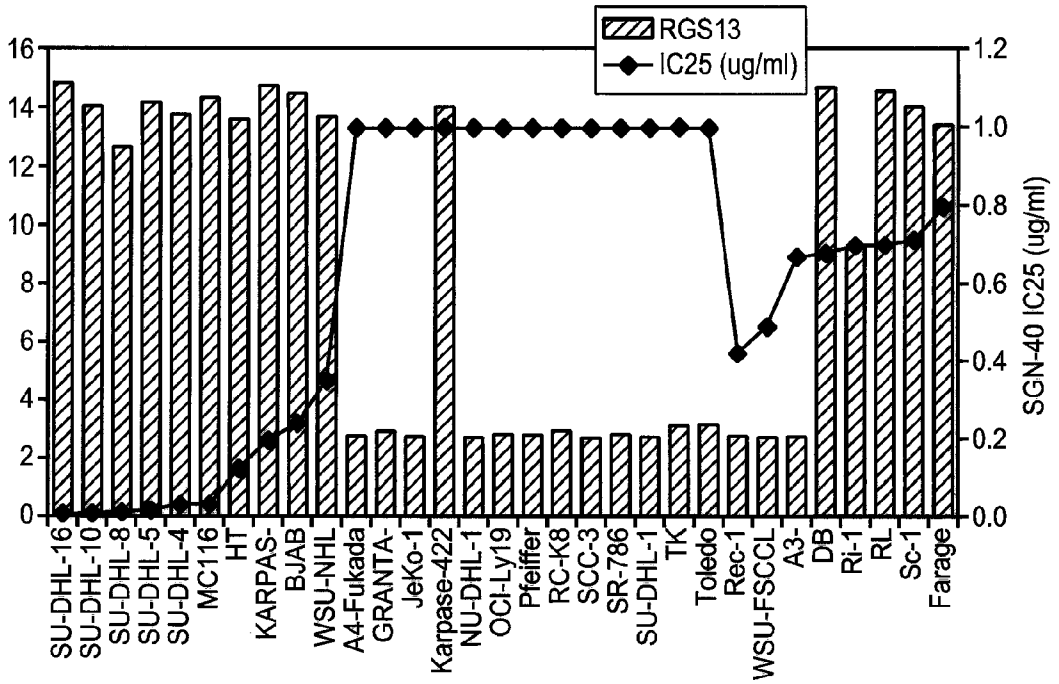

FIG. 3A

NHL Cell Lines

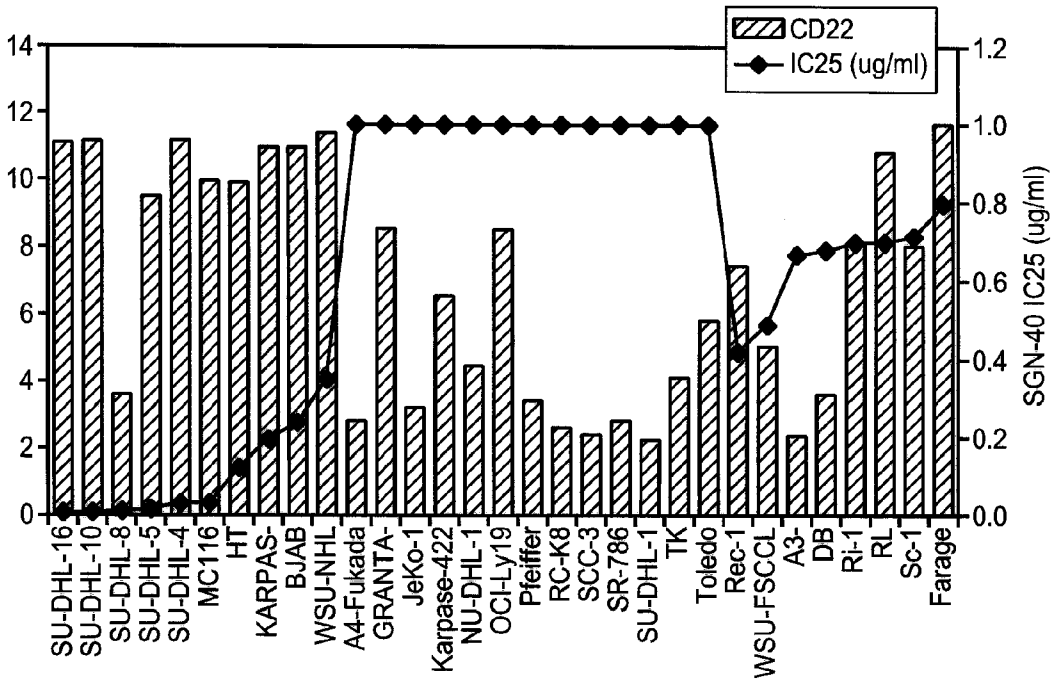

FIG. 3B

NHL Cell Lines

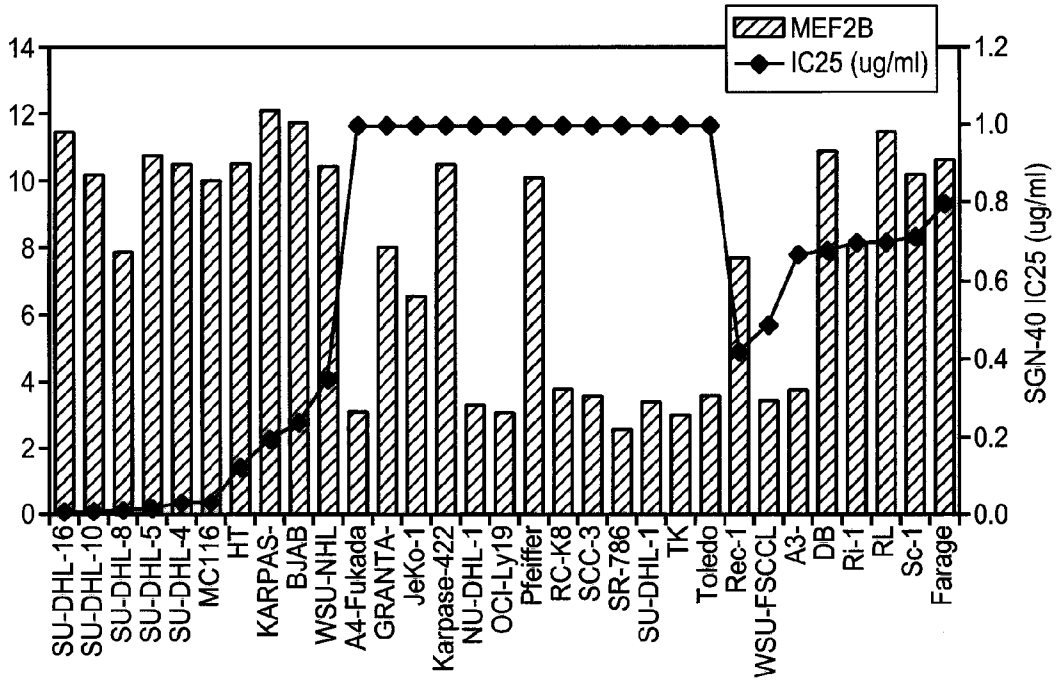

FIG. 3C

NHL Cell Lines

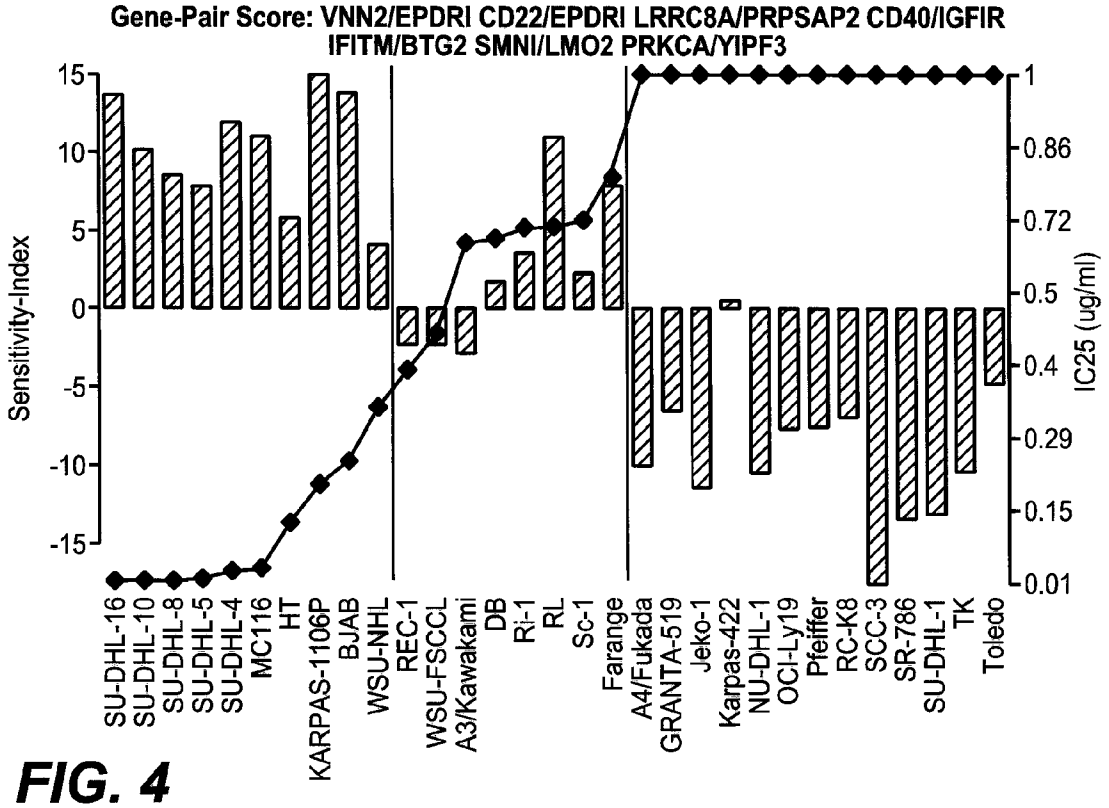
Gene-Pair Score: VNN2/EPDRI CD22/EPDRI LRRC8A/PRPSAP2 CD40/IGFIR IFITM/BTG2 SMNI/LMO2 PRKCA/YIPF3
Sensitivity-Index
IC25 (ug/ml)
15
10
5
0
-5
-10
-15
1
0.86
0.72
0.5
0.4
0.29
0.15
0.01
SU-DHL-16
SU-DHL-10
SU-DHL-8
SU-DHL-5
SU-DHL-4
MC116
HT
KARPAS-1106P
BJAB
WSU-NHL
REC-1
WSU-FSCCL
A3/Kawakami
DB
Ri-1
RL
Sc-1
Farange
A4/Fukada
GRANTA-519
Jeko-1
Karpas-422
NU-DHL-1
OCI-Ly19
Pfeiffer
RC-K8
SCC-3
SR-786
SU-DHL-1
TK
Toledo

FIG. 4

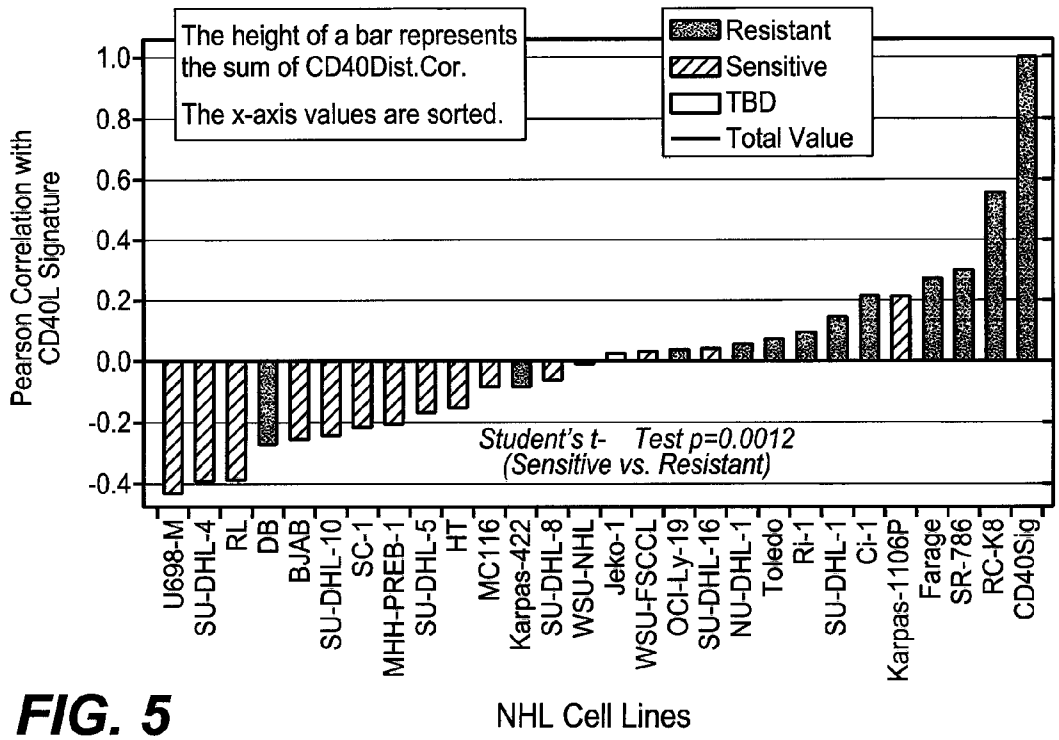
The height of a bar represents the sum of CD40Dist.Cor.
The x-axis values are sorted.
Resistant
Sensitive
TBD
Total Value
Pearson Correlation with CD40L Signature
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
Student's t- Test p=0.0012
(Sensitive vs. Resistant)
U698-M
SU-DHL-4
RL
DB
BJAB
SU-DHL-10
SC-1
MHH-PREB-1
SU-DHL-5
HT
MC116
Karpas-422
SU-DHL-8
WSU-NHL
Jeko-1
WSU-FSCCL
OCI-Ly-19
SU-DHL-16
NU-DHL-1
Toledo
Ri-1
SU-DHL-1
Ci-1
Karpas-1106P
Farage
SR-786
RC-K8
CD40Sig
NHL Cell Lines

FIG. 5

VNN2

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

```
   1 aaaccttggc catggtcact tcctcttttc caatctctgt ggcagttttt gccctaataa
  61 ccctgcaggt tggtactcag gacagtttta tagctgcagt gtatgaacat gctgtcattt
 121 tgccaaataa aacagaaaca ccagtttctc aggaggatgc cttgaatctc atgaacgaga
 181 atatagacat tctggagaca gcgatcaagc aggcagctga gcagggtgct cgaatcattg
 241 tgactccaga agatgcactt tatggatgga aatttaccag ggaaactgtt ttcccttatc
 301 tggaggatat cccagaccct caggtgaact ggattccgtg tcaagacccc cacagatttg
 361 gtcacacacc agtacaagca agactcagct gcctggccaa ggacaactct atctatgtct
 421 tggcaaattt gggggacaaa aagccatgta attcccgtga ctccacatgt cctcctaatg
 481 gctactttca atacaatacc aatgtggtgt ataatacaga aggaaaactc gtggcacgtt
 541 accataagta ccacctgtac tctgagcctc agtttaatgt ccctgaaaag ccggagttgg
 601 tgactttcaa caccgcattt ggaaggtttg gcattttcac gtgctttgat atattcttct
 661 atgatcctgg tgttaccctg gtgaaagatt tccatgtgga caccatactg tttcccacag
 721 cttggatgaa cgttttgccc cttttgacag ctattgaatt ccattcagct tgggcaatgg
 781 gaatgggagt taatcttctt gtggccaaca cacatcatgt cagcctaaat atgacaggaa
 841 gtggtattta tgcaccaaat ggtcccaaag tgtatcatta tgacatgaag acagagttgg
 901 gaaaacttct cctttcagag gtggattcac atcccctatc ctcgcttgcc tacccaacag
 961 ctgttaattg gaatgcctac gccaccacca tcaaaccatt tccagtacag aaaaacactt
1021 tcaggggatt tatttccagg gatgggttca acttcacaga acttttgaa aatgcaggaa
1081 accttacagt ctgtcaaaag gagctttgct gtcatttaag ctacagaatg ttacaaaaag
1141 aagagaatga agtatacgtt ctaggagctt ttacaggatt acatggccga aggagaagag
1201 agtactggca ggtctgcaca atgctgaagt gcaaaactac taatttgaca acttgtggac
1261 ggccagtaga aactgcttct acaagatttg aaatgttctc cctcagtggc acatttggaa
1321 cagagtatgt ttttcctgaa gtgctactta ccgaaattca tctgtcacct ggaaaatttg
1381 aggtgctgaa agatgggcgt ttggtaaaca agaatggatc atctgggcct atactaacag
1441 tgtcactctt tgggaggtgg tacacaaagg actcacttta cagctcatgt gggaccagca
1501 attcagcaat aacttacctg ctaatattca tattattaat gatcatagct ttgcaaaata
1561 ttgtaatgtt atagggcgtc tctttatcac tcagcttctg catcatatgc ttggctgaat
1621 gtgtttatcg gcttcccaag tttactaaga aactttgaag ggctatttca gtagtataga
1681 ccagtgagtc ctaaatattt tttctcatca ataattattt tttaagtatt atgataatgt
1741 tgtccatttt tttggctact ctgaaatgtt gcagtgtgga acaatggaaa gagcctgggt
1801 gtttgggtca gataaatgaa gatcaaactc cagctccagc ctcatttgct 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 atggaatgtt
      181 tccacatatt ataccaccaa catgagaaaa aaatgatcat tgtttatttg aagcttgatg
      241 atattctaac gctgcctttt ctcttctcat tttagagaaa aatgagcagg cggaattgtt
      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 agtggtgggt ttgatctttt tatttagaaa cccacaaaat
      841 cagaaacaca gtacaaataa aacagaaatc aaactataag ttgactttta gttcctaaaa
      901 agaaacatat ttcaaaagca atggaatcta gaattcttat aacatgaata acaaaatgta
      961 cagcaagcct atgtagttca attaatatat aaggaaaagg aaggtctttc ttcatgatac
     1021 aagcattata aagtttttac tgtagtagtc aattaatgga tatttccttg ttaataaaat
     1081 tttgtgtcat aatttacaaa ttagttcttt aaaaattgtt gttatatgaa ttgtgtttct
     1141 agcatgaatg ttctatagag tactctaaat aacttgaatt tatagacaaa tgctactcac
     1201 agtacaatca attgtattat accatgagaa aatcaaaaag gtgttcttca gagacatttt
     1261 atctataaaa ttttcctact attatgttca ttaacaaact tctttatcac atgtatcttc
     1321 tacatgtaaa acatttctga tgatttttta acaaaaaata tatgaatttc ttcatttgct
     1381 cttgcatcta cattgctata aggatataaa atgtggtttc tatattttga gatgtttttt
     1441 ccttacaatg tgaactcatc gtgatcttgg aaatcaataa agtcaaatat caactaaa
```

Figure 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 gtgagggaag acacgcggaa acaggcttgc acccagacac gacaccatgc
       61 atctcctcgg cccctggctc ctgctcctgg ttctagaata cttggctttc tctgactcaa
      121 gtaaatgggt ttttgagcac cctgaaaccc tctacgcctg ggaggggggcc tgcgtctgga
      181 tcccctgcac ctacagagcc ctagatggtg acctggaaag cttcatcctg ttccacaatc
      241 ctgagtataa caagaacacc tcgaagtttg atgggacaag actctatgaa agcacaaagg
      301 atgggaaggt tccttctgag cagaaaaggg tgcaattcct gggagacaag aataagaact
      361 gcacactgag tatccacccg gtgcacctca atgacagtgg tcagctgggg ctgaggatgg
      421 agtccaagac tgagaaatgg atggaacgaa tacacctcaa tgtctctgaa aggccttttc
      481 cacctcatat ccagctccct ccagaaattc aagagtccca ggaagtcact ctgacctgct
      541 tgctgaattt ctcctgctat gggtatccga tccaattgca gtggctccta gaggggttc
      601 caatgaggca ggctgctgtc acctcgacct ccttgaccat caagtctgtc ttcacccgga
      661 gcgagctcaa gttctcccca cagtggagtc accatgggaa gattgtgacc tgccagcttc
      721 aggatgcaga tgggaagttc ctctccaatg acacggtgca gctgaacgtg aagcacaccc
      781 cgaagttgga gatcaaggtc actcccagtg atgccatagt gagggagggg gactctgtga
      841 ccatgacctg cgaggtcagc agcagcaacc cggagtacac gacggtatcc tggctcaagg
      901 atgggacctc gctgaagaag cagaatacat tcacgctaaa cctgcgcgaa gtgaccaagg
      961 accagagtgg gaagtactgc tgtcaggtct ccaatgacgt gggcccggga aggtcggaag
     1021 aagtgttcct gcaagtgcag tatgccccgg aaccttccac ggttcagatc ctccactcac
     1081 cggctgtgga gggaagtcaa gtcgagtttc tttgcatgtc actggccaat cctcttccaa
     1141 caaattacac gtggtaccac aatgggaaag aaatgcaggg aaggacagag gagaaagtcc
     1201 acatcccaaa gatcctcccc tggcacgctg ggacttattc ctgtgtggca gaaaacattc
     1261 ttggtactgg acagaggggc ccgggagctg agctggatgt ccagtatcct cccaagaagg
     1321 tgaccacagt gattcaaaac cccatgccga ttcgagaagg agacacagtg acccttttct
     1381 gtaactacaa ttccagtaac cccagtgtta cccggtatga atggaaaccc catggcgcct
     1441 gggaggagcc atcgcttggg gtgctgaaga tccaaaacgt tggctgggac aacacaacca
     1501 tcgcctgcgc acgttgtaat agttggtgct cgtgggcctc ccctgtcgcc ctgaatgtcc
     1561 agtatgcccc ccgagacgtg agggtccgga aaatcaagcc cctttccgag attcactctg
     1621 gaaactcggt cagcctccaa tgtgacttct caagcagcca ccccaaagaa gtccagttct
     1681 tctgggagaa aaatggcagg cttctgggga aagaaagcca gctgaatttt gactccatct
     1741 ccccagaaga tgctgggagt tacagctgct gggtgaacaa ctccatagga cagacagcgt
     1801 ccaaggcctg gacacttgaa gtgctgtatg cacccaggag gctgcgtgtg tccatgagcc
     1861 cgggggacca agtgatggag gggaagagtg caaccctgac ctgtgagagt gacgccaacc
     1921 ctcccgtctc ccactacacc tggtttgact ggaataacca aagcctcccc caccacagcc
     1981 agaagctgag attggagccg gtgaaggtcc agcactcggg tgcctactgg tgccagggga
     2041 ccaacagtgt gggcaagggc cgttcgcctc tcagcaccct tactgtctac tatagcccgg
     2101 agaccatcgg caggcgagtg gctgtgggac tcgggtcctg cctcgccatc ctcatcctgg
     2161 caatctgtgg gctcaagctc cagcgacgtt ggaagaggac acagagccag caggggcttc
     2221 aggagaattc cagcggccag agcttctttg tgaggaataa aaaggttaga agggcccccc
     2281 tctctgaagg cccccactcc ctgggatgct acaatccaat gatggaagat ggcattagct
     2341 acaccaccct gcgctttccc gagatgaaca taccacgaac tggagatgca gagtcctcag
```

Figure 6-3

```
2401 agatgcagag acctccccgg acctgcgatg acacggtcac ttattcagca ttgcacaagc
2461 gccaagtggg cgactatgag aacgtcattc cagattttcc agaagatgag gggattcatt
2521 actcagagct gatccagttt ggggtcgggg agcggcctca ggcacaagaa aatgtggact
2581 atgtgatcct caaacattga cactggatgg gctgcagcag aggcactggg ggcagcgggg
2641 gccagggaag tccccgagtt tccccagaca ccgccacatg gcttcctcct gcgtgcatgt
2701 gcgcacacac acacacacac gcacacacac acacacacac tcactgcgga gaaccttgtg
2761 cctggctcag agccagtctt tttggtgagg gtaaccccaa acctccaaaa ctcctgcccc
2821 tgttctcttc cactctcctt gctacccaga aatcatctaa atacctgccc tgacatgcac
2881 acctcccctg ccccaccagc ccactggcca tctccacccg gagctgctgt gtcctctgga
2941 tctgctcgtc attttccttc ccttctccat ctctctggcc ctctaccccc gatctgacat
3001 ccccactcac gaatattatg cccagtttct gcctctgagg gaaagcccag aaaaggacag
3061 aaacgaagta gaaaggggcc cagtcctggc ctggcttctc ctttggaagt gaggcattgc
3121 acggggagac gtacgtatca gcggcccctt gactctgggg actccgggtt tgagatggac
3181 acactggtgt 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
       61 aagccgtggt gggatgtgtt cacagactac atctctatcg tcatgctgat gattgccgtc
      121 ttcgggggga cgctgcaggt cacccaagac aagatgatct gcctgccttg taagtgggtc
      181 accaaggact cctgcaatga ttcgttccgg ggctgggcag cccctggccc ggagcccacc
      241 taccccaact ccaccattct gccgaccccc gacacgggcc ccacaggcat caagtatgac
      301 ctggaccggc accagtacaa ctacgtggac gctgtgtgct atgagaaccg actgcactgg
      361 tttgccaagt acttccccta cctggtgctt ctgcacacgc tcatcttcct ggcctgcagc
      421 aacttctggt tcaaattccc gcgcaccagc tcgaagctgg agcactttgt gtctatcctg
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     1381 atcccgccca gcattgccca gctcacgggc ctcaaggagc tgtggctcta ccacacagcg
     1441 gccaagattg aagcgcccgc gctggccttc ctgcgcgaga acctgcgggc gctgcacatc
     1501 aagttcaccg acatcaagga gatcccgctg tggatctata gcctgaagac actggaggag
     1561 ctgcacctga cgggcaacct gagcgcggag aacaaccgct acatcgtcat cgacgggctg
     1621 cgggagctca aacgcctcaa ggtgctgcgg ctcaagagca acctaagcaa gctgccacag
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     1981 ctcaccaacc tggagcgcct ctacctgaac cgcaacaaga tcgagaagat ccccacccag
     2041 ctcttctact gccgcaagct gcgctacctg gacctcagcc acaacaacct gaccttcctc
     2101 cctgccgaca tcggcctcct gcagaacctc cagaacctag ccatcacggc caaccggatc
     2161 gagacgctcc ctccggagct cttccagtgc cggaagctgc gggccctgca cctgggcaac
     2221 aacgtgctgc agtcactgcc ctccagggtg ggcgagctga ccaacctgac gcagatcgag
     2281 ctgcggggca accggctgga gtgcctgcct gtggagctgg gcgagtgccc actgctcaag
     2341 cgcagcggct tggtggtgga ggaggacctg ttcaacacac tgccacccga 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 gccaaggctg gggcagggga gtcagcagag gcctcgctcg ggcgcccagt ggtcctgccg
       61 cctggtctca cctcgctatg gttcgtctgc ctctgcagtg cgtcctctgg ggctgcttgc
      121 tgaccgctgt ccatccagaa ccacccactg catgcagaga aaaacagtac ctaataaaca
      181 gtcagtgctg ttctttgtgc cagccaggac agaaactggt gagtgactgc acagagttca
      241 ctgaaacgga atgccttcct tgcggtgaaa gcgaattcct agacacctgg aacagagaga
      301 cacactgcca ccagcacaaa tactgcgacc ccaacctagg gcttcgggtc cagcagaagg
      361 gcacctcaga aacagacacc atctgcacct gtgaagaagg ctggcactgt acgagtgagg
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      481 ctacaggggt ttctgatacc atctgcgagc cctgcccagt cggcttcttc tccaatgtgt
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     1261 ctgcgcccag gaagccatat acacagatgc ccattgcagc attgtttgtg atagtgaaca
     1321 actggaagct gcttaactgt ccatcagcag gagactggct aaataaaatt agaatatatt
     1381 tatacaacag aatctcaaaa acactgttga gtaaggaaaa aaaggcatgc tgctgaatga
     1441 tgggtatgga acttttaaa aaagtacatg cttttatgta tgtatattgc ctatggatat
     1501 atgtataaat acaatatgca tcatatattg atataacaag ggttctggaa gggtacacag
     1561 aaaacccaca gctcgaagag tggtgacgtc 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 cacgcagaaa accacacttc tcaaaccttc actcaacact tccttcccca aagccagaag
      181 atgcacaagg aggaacatga ggtggctgtg ctgggggcac cccccagcac catccttcca
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      421 accgccaagt gcctgaacat ctgggccctg attctgggca tcctcatgac cattggattc
      481 atcctgttac tggtattcgg ctctgtgaca gtctaccata ttatgttaca gataatacag
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      601 gctggccctg cacgctgggg ctgttgcccc tgcccccttg gtcctgcccc tagatacagc
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      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)

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       61 cgggcaacga ctccacggcg tctcaggacg tggccaaccg cttcgcccgc aaaggggcgc
      121 tgaggcagaa gaacgtgcac gaggtgaagg accacaaatt catcgcgcgc ttcttcaagc
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Figure 6-8

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Figure 6-9

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8401 ttcagaatat cttttataaa cagaagcatt tgaagtcatt gcttttgcta catgatttgt
8461 gtgtgtgaag gacataccac gtttaaatca ttaattgaaa aacatcatat aagccccaac
8521 tttgtttgga ggaagagacg gaggttgagg tttttccttc tgtataagca cctactgaca
8581 aaatgtagag gccattcaac cgtcaaacac catttggtta tatcgcagag gagacggatg
8641 tgtaaattac tgcattgctt tttttttcag tttgtataac ctctaatctc cgtttgcatg
8701 atacgctttg ttagaaacat taattgtagt ttggaagcaa gtgtgtatga ataaagataa
8761 tgatcattcc aaaaaaaaaa aaaaaaa
```

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

```
       1 ggcccctcga gcctcgaacc ggaacctcca aatccgagac gctctgctta tgaggacctc
      61 gaaatatgcc ggccagtgaa aaaatcttgt ggctttgagg gcttttggtt ggccaggggc
     121 agtaaaaatc tcggagagct gacaccaagt cctcccctgc cacgtagcag tggtaaagtc
     181 cgaagctcaa attccgagaa ttgagctctg ttgattctta gaactggggt tcttagaagt
     241 ggtgatgcaa gaagtttcta ggaaaggccg gacaccaggt tttgagcaaa attttggact
     301 gtgaagcaag gcattggtga agacaaaatg gcctcgccgg ctgacagctg tatccagttc
     361 acccgccatg ccagtgatgt tcttctcaac cttaatcgtc tccggagtcg agacatcttg
     421 actgatgttg tcattgttgt gagccgtgag cagtttagag cccataaaac ggtcctcatg
     481 gcctgcagtg gcctgttcta tagcatcttt acagaccagt tgaaatgcaa ccttagtgtg
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     601 acatctcggc tcaatttgcg ggagggcaac atcatggctg tgatggccac ggctatgtac
     661 ctgcagatgg agcatgttgt ggacacttgc cggaagttta ttaaggccag tgaagcagag
     721 atggtttctg ccatcaagcc tcctcgtgaa gagttcctca acagccggat gctgatgccc
     781 caagacatca tggcctatcg gggtcgtgag gtggtggaga acaacctgcc actgaggagc
     841 gcccctgggt gtgagagcag agcctttgcc cccagcctgt acagtggcct gtccacaccg
     901 ccagcctctt attccatgta cagccacctc cctgtcagca gcctcctctt ctccgatgag
     961 gagtttcggg atgtccggat gcctgtggcc aaccccttcc ccaaggagcg ggcactccca
    1021 tgtgatagtg ccaggccagt ccctggtgag tacagccggc cgactttgga ggtgtccccc
    1081 aatgtgtgcc acagcaatat ctattcaccc aaggaaacaa tcccagaaga ggcacgaagt
    1141 gatatgcact acagtgtggc tgagggcctc aaacctgctg ccccctcagc ccgaaatgcc
    1201 ccctacttcc cttgtgacaa ggccagcaaa gaagaagaga gaccctcctc ggaagatgag
    1261 attgccctgc atttcgagcc ccccaatgca cccctgaacc ggaagggtct ggttagtcca
    1321 cagagccccc agaaatctga ctgccagccc aactcgccca cagagtcctg cagcagtaag
    1381 aatgcctgca tcctccaggc ttctggctcc cctccagcca agagccccac tgaccccaaa
    1441 gcctgcaact ggaagaaata caagttcatc gtgctcaaca gcctcaacca gaatgccaaa
    1501 ccagaggggc ctgagcaggc tgagctgggc cgcctttccc cacgagccta cacggcccca
    1561 cctgcctgcc agccacccat ggagcctgag aaccttgacc tccagtcccc aaccaagctg
    1621 agtgccagcg gggaggactc caccatccca caagccagcc ggctcaataa catcgttaac
    1681 aggtccatga cgggctctcc ccgcagcagc agcgagagcc actcaccact ctacatgcac
    1741 cccccgaagt gcacgtcctg cggctctcag tccccacagc atgcagagat gtgcctccac
    1801 accgctggcc ccacgttccc tgaggagatg ggagagaccc agtctgagta ctcagattct
    1861 agctgtgaga acggggcctt cttctgcaat gagtgtgact gccgcttctc tgaggaggcc
    1921 tcactcaaga ggcacacgct gcagacccac agtgacaaac cctacaagtg tgaccgctgc
    1981 caggcctcct tccgctacaa gggcaacctc gccagccaca agaccgtcca taccggtgag
    2041 aaaccctatc gttgcaacat ctgtggggcc cagttcaacc ggccagccaa cctgaaaacc
    2101 cacactcgaa ttcactctgg agagaagccc tacaaatgcg aaacctgcgg agccagattt
    2161 gtacaggtgg cccacctccg tgcccatgtg cttatccaca ctggtgagaa gccctatccc
    2221 tgtgaaatct gtggcacccg tttccggcac cttcagactc tgaagagcca cctgcgaatc
    2281 cacacaggag agaaacctta ccattgtgag aagtgtaacc tgcatttccg tcacaaaagc
    2341 cagctgcgac ttcacttgcg ccagaagcat ggcgccatca ccaacaccaa ggtgcaatac
```

Figure 6-11

```
2401 cgcgtgtcag ccactgacct gcctccggag ctccccaaag cctgctgaag catggagtgt
2461 tgatgctttc gtctccagcc ccttctcaga atctacccaa aggatactgt aacactttac
2521 aatgttcatc ccatgatgta gtgcctcttt catccactag tgcaaatcat agctgggggt
2581 tgggggtggt gggggtcggg gcctggggga ctgggagccg cagcagctcc ccctccccca
2641 ctgccataaa acattaagaa aatcatattg cttcttctcc tatgtgtaag gtgaaccatg
2701 tcagcaaaaa gcaaaatcat tttatatgtc aaagcagggg agtatgcaaa agttctgact
2761 tgactttagt ctgcaaaatg aggaatgtat atgttttgtg ggaacagatg tttcttttgt
2821 atgtaaatgt gcattctttt aaaagacaag acttcagtat gttgtcaaag agagggcttt
2881 aatttttta accaaaggtg aaggaatata tggcagagtt gtaaatatat aaatatatat
2941 atatataaaa taaatatata taaacctaac aaagatatat taaaaatata aaactgcgtt
3001 aaaggctcga ttttgtatct gcaggcagac acggatctga gaatctttat tgagaaagag
3061 cacttaagag aatattttaa gtattgcatc tgtataagta agaaaatatt ttgtctaaaa
3121 tgcctcagtg tatttgtatt tttttgcaag tgaaggttta caatttacaa agtgtgtatt
3181 aaaaaaaaca aaaagaacaa aaaaatctgc agaaggaaaa atgtgtaatt ttgttctagt
3241 tttcagtttg tatatacccg tacaacgtgt cctcacggtg cctttttca cggaagtttt
3301 caatgatggg cgagcgtgca ccatcccttt ttgaagtgta ggcagacaca gggacttgaa
3361 gttgttacta actaaactct ctttgggaat gtttgtctca tcccattctg cgtcatgctt
3421 gtgttataac tactccggag acagggtttg gctgtgtcta aactgcatta ccgcgttgta
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

```
       1 tccccccctct taaaacacga tgcctcccag gatgctagtg gcaccactgc cactgcattt
      61 cctgctggca gcagtgagca gtgaaaaccg aagcggcaga aggcagtggc agcaggcagt
     121 ggcagcaggc agtggcccag gcagaaatag ctcccgcgcg attcactgga gccttccccg
     181 ggccctggtc ccggctaccg ggactcgcgc gtccggatct caaaagcggc agaggccacc
     241 gaagggacag gaagcacttt ggtccagacc acactcccgg cacagtgcgg aaagagccgg
     301 cgggagccac tctgatcccg gacgcctcag cgcccccttg ggcttgggct tgccctcggg
     361 ccggggaagg ctgaccgcga tgccaggacg cgctcccctc cgcaccgtcc cgggcgccct
     421 gggtgcctgg ctgctgggcg gcctctgggc ctggaccctg tgcggcctgt gcagcctggg
     481 ggcggtggga gccccgcgcc cgtgccaggc gccgcagcag tgggaggggc gccaggttat
     541 gtaccagcaa agtagcgggc gcaacagccg cgccctgctc tcctacgacg ggctcaacca
     601 gcgcgtgcgg gtgctggacg agaggaaggc gctgatcccc tgcaagagat tatttgaata
     661 tattttgctg tataaggatg gagtgatgtt tcagattgac caagccacca agcagtgctc
     721 aaagatgacc ctgacacagc cctgggatcc tcttgacatt cctcaaaact ccacctttga
     781 agaccagtac tccatcgggg ggcctcagga gcagatcacc gtccaggagt ggtcggacag
     841 aaagtcagct agatcctatg aaacctggat tggcatctat acagtcaagg attgctatcc
     901 tgtccaggaa acctttacca taaactacag tgtgatattg tctacgcggt tttttgacat
     961 ccagctgggt attaaagacc cctcggtgtt taccctcca agcacgtgcc agatggccca
    1021 actggagaag atgagcgaag actgctcctg gtgagcctgt gcatagggaa gcggcagcat
    1081 cggatgtcag ccccctgcgg ccccagctgg agatggatat gagactagtc aagatgtgaa
    1141 tgctaattgg agagaaatat aattttagga agatgcacat tgatgtgggg ttttgatgtg
    1201 tctgattttg actactcaag ctctgtttac agaagaaaat tgaatggcga gggtgtggcc
    1261 atatgaactg actagatggc taatatggac actttgggta tttctaatgc ctgttcaggg
    1321 ctggtttttct gcatgcacgg gtatacacat aatgcagtgc catgcacata gggaagggtc
    1381 agtaagagaa gtttgccttg gcagcaagta tttattgttg acattattca gaattagtga
    1441 taataaaaag cagagtgatt ttggtcaatt ttattattaa ttcttaaatt ccctgcagag
    1501 aatgcccccct ttattgctgc accagggttg gcattgctcc cactgagccc tactccaccc
    1561 tgtccctgca ctcccttggt tgccaaaaaa atgataactt aaatcccttc cagacttaag
    1621 aattttatgg catggcccaa ttgatataaa catttagaag gaaatgaaaa gctaaaatag
    1681 gaagtaatta ttcctctaaa gaaacatttt gagcaaggca gtttagagaa tcctaatgtc
    1741 tacactggca tagcacgagc catgtaagct tctttttttt ctatgcaaga gtattgatgt
    1801 atgtgctgaa tcttcacaga cttgtcaata cacaggcagt attctaaaat agcactgaac
    1861 agggagtcag gagactattg tctcctaaac ccaggactag agttccctcg tactgtcact
    1921 cctttggtca ttaaatgcac tgggcttgcc cgcactttgg ccttcctaga acactgcttc
    1981 ataacctctc tgtctgactt ctgcatctcc ttccaggtca gctcattcac aagagttgct
    2041 cccaagcctg gatgagttgc accttgcatc ttgagcatgc atttctcaca ataattatta
    2101 agctgtgtga taatttctgc tttcaggaca ctcatccatt atcttggctg tgagctcctt
    2161 gggtacgggt accttgtatg tttacttta tatccctagc acaaagcaag tgcctggcac
    2221 atagtcagtg ccctaagtat tcgtagagtg aagaatgcca gcctctcttg tccctggttt
    2281 ccttatgtgt tgaatgtggt tgagtttgtc cattgctagg gagagacttc cagtaataaa
    2341 atttactatt ctagatgctt ctactgttat gttttatctg cccatttatc tttcttagtt
    2401 accaggagaa atgtgtgaca cctatattat aatgaaaaca atctcattac ttatagttta
    2461 tctatattaa acaaatttaa ttgcatttta aagcattctt tgatactgtt gcttttgcaa
    2521 taaatatgga taatcttggt tataagggag ttaaaacaat gctgtaataa ataaagtgct
    2581 tcatgtgatc aaaatcaaaa aaaaaaaaaa aaa
```

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
      1 ctagagaggc cgccaggaga cccggcgctt tcttccttct gcagctgagg ctgcggcggg
     61 gccggggctg gggtcggggc caggaggaat tttgttgtca gagaataaaa ggaggttgtc
    121 cataattgac tttaagcagc aatcagtaaa acattgagct cttcagctcc gcctttcttg
    181 ctctgaaaat tggaaaacca agaaggtttt gatgttttgt gtgacgccac ctgaattaga
    241 aaccaagatg aacataacca aaggtggtct ggtgttgttt tcagcaaact cgaattcatc
    301 atgtatggag ctatcaaaga aaattgcaga gcggctaggg gtggagatgg gcaaagtgca
    361 ggtttaccag gaacctaaca gagaaacaag agtacaaatt caagagtctg tgaggggaaa
    421 agatgttttc atcatccaaa ctgtttcgaa ggacgtgaac accaccatca tggagctcct
    481 gatcatggtg tatgcatgta agacctcttg tgccaagagc atcattggcg tgatacccta
    541 ctttccttac agcaagcagt gcaagatgag aaaaagaggc tccattgtct ctaaattgct
    601 ggcttccatg atgtgcaaag ctggtctaac tcatcttatt actatggatt tacaccagaa
    661 ggaaattcag ggcttcttca atattcctgt tgacaattta agagcatctc ccttcttatt
    721 acagtatatt caagaagaga tcccagatta caggaatgca gtaatcgtgg ccaagtctcc
    781 agcctcggcg aagagggcac agtcttttgc tgagcgcctg cgcctgggaa ttgcagtgat
    841 tcatggagag gcgcaggatg ccgagtcgga cttggtggat ggacggcatt ccccacccat
    901 ggtcagaagt gtggctgcca tccaccccag cctggagatc cccatgctga ttcctaaaga
    961 aaagccccca atcacggttg tgggtgatgt tggaggaagg attgccatca tcgtggatga
   1021 catcattgat gatgttgaca gctttcttgc tgcagcagag accctgaagg aaagaggtgc
   1081 atataagatc tttgtgatgg caactcatgg cttgttgtct tctgacgccc cccggcggat
   1141 tgaagagtct gccattgatg aggtggtggt caccaataca attccacatg aagtccagaa
   1201 gctccagtgc cccaagatta aaactgtgga tatcagcatg atcctttcag aggcgatccg
   1261 tcggatccac aatggggagt ccatgtccta ccttttcaga aacataggct tagatgactg
   1321 agttttcctt taggaaaact cccgagggcc aaactggaaa cataagagtg actgctcggt
   1381 gggatggatt tcacaggaac cgtcatgctt gttcctccct ctcccctgta acctcacttc
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   1501 gggagcaatt tttataaaag aaaaacttta ttctcctctt ttgaaaaggt aagacctcgt
   1561 tttagttgta actgtttaaa aaataacact tggaataaga tttgtaagct cacaaagcct
   1621 tcttccaaag ttgcttgagc caagtgctta aaaagttaat aaaataaaat gatctgtatg
   1681 atacctgcaa ttgaaaagcc gaaaagatta tactgtcaag tccagtaaat gacattttta
   1741 gagatgcttt tgtagacaag catatggaat atgtgattgt atttatttttc tgcaactaaa
   1801 aaaggaataa aaacttgtgt ttgtgtgttt ttctaaaact ttgtgttttg gcaatcgttt
   1861 tataactaaa ataaaatgaa agctaaatct
```

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
        1 ttttttttttt ttttttttga gaaaggggaa tttcatccca aataaaagga atgaagtctg
       61 gctccggagg agggtccccg acctcgctgt gggggctcct gtttctctcc gccgcgctct
      121 cgctctggcc gacgagtgga gaaatctgcg ggccaggcat cgacatccgc aacgactatc
      181 agcagctgaa gcgcctggag aactgcacgg tgatcgaggg ctacctccac atcctgctca
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      301 acttgctgct gttccgagtg gctggcctcg agagcctcgg agacctcttc cccaacctca
      361 cggtcatccg cggctggaaa ctcttctaca actacgccct ggtcatcttc gagatgacca
      421 atctcaagga tattgggctt tacaacctga ggaacattac tcgggggccc atcaggattg
      481 agaaaaatgc tgacctctgt tacctctcca ctgtggactg gtccctgatc ctggatgcgg
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```

Figure 6-15

```
2461 acagctgcaa ccacgaggct gagaagctgg gctgcagcgc ctccaacttc gtctttgcaa
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4561 gtggctgtcc ctgtggcccc atccaaccac tgtacacacc cgcctgacac cgtgggtcat
4621 tacaaaaaaa cacgtggaga tggaaatttt taccttatc tttcaccttt ctagggacat
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5581 ataatttgcc atgaactgtt ggatgccttt ttataaatac atcccccatc cctgctccca
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Figure 6-16

```
5641 cctgcccctt tagttgtttt ctaacccgta ggctctctgg gcacgaggca gaaagcaggc
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5761 cctgttacag tgcaagacat gatacaaact caggtcagaa aaacaaaggt taaatatttc
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6361 ttttagcact tctcaccaga gagatgacag cacaagagtt gcttctggga tagaaatgtt
6421 taggagtaag aacaaagctg ggatacggtg attgctagtt gtgactgaag attcaacaca
6481 gaaaagaaag tttatacggc ttttttgctg gtcagcagtt tgtcccactg ctttctctag
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8341 tgaaccactg aggcacatca tggaattgat gtgagcatta agacgttctc ccacacagcc
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8461 cagaccaccc caggtctcct tcgtgggatg tcatgacgtt tgacatacct ttggaacgag
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8581 tcttaagatg cggagtcaca tttcaatggt acgaaaagtg gcttcgtaaa atagaagagc
8641 agtcactgtg gaactaccaa atggcgagat gctcggtgca cattggggtg ctttgggata
8701 aaagatttat gagccaacta ttctctggca ccagattcta ggccagtttg ttccactgaa
8761 gcttttccca cagcagtcca cctctgcagg ctggcagccg aatggcttgc cagtggctct
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Figure 6-17

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 8941 acaggcgccc tcctggtgac agtgacccgc cgtggtatgc cttggcccat tccagcagtc
 9001 ccagttatgc atttcaagtt tggggtttgt tcttttcgtt aatgttcctc tgtgttgtca
 9061 gctgtcttca tttcctgggc taagcagcat tgggagatgt ggaccagaga tccactcctt
 9121 aagaaccagt ggcgaaagac actttctttc ttcactctga agtagctggt ggtacaaatg
 9181 agaacttcaa gagaggatgt tatttagact gaacctctgt tgccagagat gctgaagata
 9241 cagaccttgg acaggtcaga gggtttcatt tttggccttc atcttagatg actggttgcg
 9301 tcatttggag aagtgagtgc tccttgatgg tggaatgacc gggtggtggg tacagaacca
 9361 ttgtcacagg gatcctggca cagagaagag ttacgagcag cagggtgcag ggcttggaag
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 9781 tggtttacaa gaactaatta aatgtttcat tgcatttttg taagaacaga ataatttat
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11041 aaaaatttca aaatgttttt gtatattctg ttgtaagaat ttattcctgt tattgcgata
11101 tactctggat tctttacata atggaaaaaa gaaactgtct attttgaatg gctgaagcta
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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
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       61 ccgcgcgcga catgagccac gggaagggaa ccgacatgct cccggagatc gccgccgccg
      121 tgggcttcct ctccagcctc ctgaggaccc ggggctgcgt gagcgagcag aggcttaagg
      181 tcttcagcgg ggcgctccag gaggcactca cagagcacta caaacaccac tggtttcccg
      241 aaaagccgtc caagggctcc ggctaccgct gcattcgcat caaccacaag atggacccca
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      961 tcagagctct ctgtctcccc cagccagaca cctgcatccc tggctcctct attactcagg
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     1201 ggaatctaaa gctttgggtt ttctgagggg ggggaggagg gaactggagg ttattggggt
     1261 taggatggaa gggaactctg cacaaaacct ttgctttgct agtgctgctt tgtgtgtatg
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     1381 ggggatgttt tttggccaaa actcttcctt ttggaaccac atgaaagtct tgatgctgct
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     1501 gccttctttt caaaagcaca actctcctct aaccctcccc tccccttcc cttctggtcg
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     2281 ttgccttccc agacctgctt ccagtcttta ttgctttaaa gttcactttg ggcccacaga
     2341 cccaagagct aattttctgg tttgtgggtt gaaacaaagc tgtgaatcac tgcaggctgt
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Figure 6-19

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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 aaaaaaaa
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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

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      61 agttaggatt tgggtcctgc agggcttgct aaggaatccc ctgatggcct aggattccac
     121 gcagagcaca tctggtgtga gagagctcgc tgcaagggtg aaggctccgc cctatcagat
     181 agacaaccag gccaccaaga ggcccagccc tccaaaccct ggatttgcaa catcctcaaa
     241 gaacagcaac gggccttgag cagaattgag aaggaaatac ccccacctgc cctcagccgt
     301 taagtgggct ttgctattca caagggcctc tgggtgtcct ggcagagagg ggagatggca
     361 caggcaccag gtgctagggt gccagggcct cccgagaagg aacaggtgca aagcaggcaa
     421 ttagcccaga aggtatccgt ggggcaggca gcctagatct gatgggggaa gccaccagga
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     541 gtagctagtg gagaggcagg aaaaaggaaa tgaaacagag acagagggaa gcctgagcca
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    2161 acagattgtt tctatacaaa tataaatctt aaaaagttgt tcaactattt tattatccta
    2221 gattatatca aagtatttgt cgtgtgtaga aaaaaaaaac agctctgcag gcttaataaa
    2281 aatgacagac tgaaaaaaaa 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
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       61 cggaggccca catcttgccc actccgcgcg cggggctagc gcgggtttca gcgacgggag
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      361 ggagagttcc tgggcatgaa gggctttaag ggacagctga gccggcaggt ggcagatcag
      421 atgtggcagg ctgggaaaag acaagcctcc agggccttca gcttgtacgc caacatcgac
      481 atcctcagac cctactttga tgtggagcct gctcaggtgc gaagcaggct cctggagtcc
      541 atgatcccta tcaagatggt caacttcccc cagaaaattg caggtgaact ctatggacct
      601 ctcatgctgg tcttcactct ggttgctatc ctactccatg ggatgaagac gtctgacact
      661 attatccggg agggcaccct gatgggcaca gccattggca cctgcttcgg ctactggctg
      721 ggagtctcat ccttcattta cttccttgcc tacctgtgca acgcccagat caccatgctg
      781 cagatgttgg cactgctggg ctatggcctc tttgggcatt gcattgtcct gttcatcacc
      841 tataatatcc acctccacgc cctcttctac ctcttctggc tgttggtggg tggactgtcc
      901 acactgcgca tggtagcagt gttggtgtct cggaccgtgg gccccacaca gcggctgctc
      961 ctctgtggca ccctggctgc cctacacatg ctcttcctgc tctatctgca ttttgcctac
     1021 cacaaagtgg tagaggggat cctggacaca ctggagggcc ccaacatccc gcccatccag
     1081 agggtcccca gagacatccc tgccatgctc cctgctgctc ggcttcccac caccgtcctc
     1141 aacgccacag ccaaagctgt tgcggtgacc ctgcagtcac actgacccca 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 gagaacccct ccccacctac
     1441 cccttccttc ctctttatct ctcccacatt 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 gcactgataa aagcatatga taaagctgtg gcttcattta agcatgctct
      181 aaagaatggt gacatttgtg aaacttcggg taaaccaaaa accacaccta aaagaaaacc
      241 tgctaagaag aataaaagcc aaaagaagaa tactgcagct tccttacaac agtggaaagt
      301 tggggacaaa tgttctgcca tttggtcaga agacggttgc atttacccag ctaccattgc
      361 ttcaattgat tttaagagag aaacctgtgt tgtggtttac actggatatg gaaatagaga
      421 ggagcaaaat ctgtccgatc tactttcccc aatctgtgaa gtagctaata atatagaaca
      481 aaatgctcaa gagaatgaaa atgaaagcca agtttcaaca gatgaaagtg agaactccag
      541 gtctcctgga aataaatcag ataacatcaa gcccaaatct gctccatgga actcttttct
      601 ccctccacca ccccccatgc cagggccaag actgggacca ggaaagccag gtctaaaatt
      661 caatggccca ccaccgccac cgccaccacc accaccccac ttactatcat gctggctgcc
      721 tccatttcct tctggaccac caataattcc cccaccacct cccatatgtc cagattctct
      781 tgatgatgct gatgctttgg gaagtatgtt aatttcatgg 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 tggggtgggg gtgggaggcc agcacggtgg tgaggcagtt gagaaaattt gaatgtggat
     1201 tagattttga atgatattgg ataattattg gtaattttta tgagctgtga gaagggtgtt
     1261 gtagtttata aaagactgtc ttaatttgca tacttaagca tttaggaatg aagtgttaga
     1321 gtgtcttaaa atgtttcaaa tggtttaaca aaatgtatgt gaggcgtatg tggcaaaatg
     1381 ttacagaatc taactggtgg acatggctgt tcattgtact gtttttttct atcttctata
     1441 tgtttaaaag tatataataa aaatatttaa ttttttttta aaaaaaaaaa aaaaaaaaca
     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 cagagcggtg accatggcca ggctggcgtt gtctcctgtg cccagccact
 121 ggatggtggc gttgctgctg ctgctctcag ctgagccagt accagcagcc agatcggagg
 181 accggtaccg gaatcccaaa ggtagtgctt gttcgcggat 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 tcggaggtct
 481 accagggctg cggcacagag ctgcgagtca tgggattcag caccttggca cagctgaagc
 541 agaggaacac gctgaaggat ggtatcatca tgatccagac gctgctgatc atcctcttca
 601 tcatcgtgcc tatcttcctg ctgctggaca aggatgacag caaggctggc atggaggaag
 661 atcacaccta cgagggcctg gacattgacc agacagccac ctatgaggac atagtgacgc
 721 tgcggacagg ggaagtgaag tggtctgtag gtgagcaccc aggccaggag tgagagccag
 781 gtcgccccat gacctgggtg caggctccct ggcctcagtg actgcttcgg agctgcctgg
 841 ctcatggccc aacccctttc ctggaccccc cagctggcct ctgaagctgg cccaccagag
 901 ctgccatttg tctccagccc ctggtcccca gctcttgcca aagggcctgg agtagaagga
 961 caacagggca gcaacttgga gggagttctc tggggatgga cgggacccag ccttctgggg
1021 gtgctatgag gtgatccgtc cccacacatg ggatggggga ggcagagact ggtccagagc
1081 ccgcaaatgg actcggagcc gagggcctcc cagcagagct tgggaagggc catggaccca
1141 actgggcccc agaagagcca caggaacatc attcctctcc cgcaaccact cccaccccag
1201 ggaggccctg gcctccagtg ccttcccccg tggaataaac 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 ccgacccacg tccctggcag ccccgattat ttacagcctc
 121 agcagagcac ggggcggggg cagaggggcc cgcccgggag ggctgctact tcttaaaacc
 181 tctgcgggct gcttagtcac agcccccctt gcttgggtgt gtccttcgct cgctccctcc
 241 ctccgtctta ggtcactgtt ttcaacctcg aataaaaact gcagccaact tccgaggcag
 301 cctcattgcc cagcggaccc cagcctctgc caggttcggt ccgccatcct cgtcccgtcc
 361 tccgccggcc cctgccccgc gcccagggat cctccagctc ctttcgcccg cgccctccgt
 421 tcgctccgga caccatggac aagttttggt ggcacgcagc ctggggactc tgcctcgtgc
 481 cgctgagcct ggcgcagatc gatttgaata taacctgccg ctttgcaggt gtattccacg
 541 tggagaaaaa tggtcgctac agcatctctc ggacggaggc cgctgacctc tgcaaggctt
 601 tcaatagcac cttgcccaca atggcccaga tggagaaagc tctgagcatc ggatttgaga
 661 cctgcaggta tgggttcata gaagggcacg tggtgattcc ccggatccac 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 ccccagcaac cctactgatg
 961 atgacgtgag cagcggctcc tccagtgaaa ggagcagcac ttcaggaggt tacatctttt
1021 acacctttcc tactgtacac cccatcccag acgaagacag tccctggatc accgacagca
1081 cagacagaat ccctgctacc actttgatga gcactagtgc tacagcaact gagacagcaa
1141 ccaagaggca agaaacctgg gattggtttt catggttgtt 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 gaacccagaa gcacaccctc ccctcattca ccatgagcat catgaggaag
1561 aagagacccc acattctaca agcacaatcc aggcaactcc tagtagtaca acggaagaaa
1621 cagctaccca gaaggaacag tggtttggca acagatggca tgagggatat cgccaaacac
1681 ccaaagaaga ctcccattcg acaacaggga cagctgcagc ctcagctcat accagccatc
1741 caatgcaagg aaggacaaca ccaagcccag aggacagttc ctggactgat ttcttcaacc
1801 caatctcaca ccccatggga cgaggtcatc aagcaggaag aaggatggat atggactcca
1861 gtcatagtat aacgcttcag cctactgcaa atccaaacac aggtttggtg gaagatttgg
1921 acaggacagg acctctttca atgacaacgc agcagagtaa ttctcagagc ttctctacat
1981 cacatgaagg cttggaagaa gataaagacc atccaacaac ttctactctg acatcaagca
2041 ataggaatga tgtcacaggt ggaagaagag acccaaatca ttctgaaggc tcaactactt
2101 tactggaagg ttatacctct cattacccac acacgaagga aagcaggacc ttcatcccag
2161 tgacctcagc taagactggg tcctttggag ttactgcagt tactgttgga gattccaact
2221 ctaatgtcaa tcgttcctta tcaggagacc aagacacatt ccaccccagt ggggggtccc
2281 ataccactca tggatctgaa tcagatggac actcacatgg gagtcaagaa ggtggagcaa
2341 acacaacctc tggtcctata aggacacccc aaattccaga atggctgatc atcttggcat
2401 ccctcttggc cttggctttg attcttgcag tttgcattgc agtcaacagt cgaagaaggt
2461 gtgggcagaa gaaaaagcta gtgatcaaca gtggcaatgg agctgtggag gacagaaagc
2521 caagtggact caacggagag gccagcaagt ctcaggaaat ggtgcatttg gtgaacaagg
2581 agtcgtcaga aactccagac cagtttatga cagctgatga gacaaggaac ctgcagaatg
2641 tggacatgaa gattggggtg taacacctac accattatct tggaaagaaa caaccgttgg
```

Figure 6-25

```
2701 aaacataacc attacaggga gctgggacac ttaacagatg caatgtgcta ctgattgttt
2761 cattgcgaat ctttttagc ataaaatttt ctactctttt tgtttttgt gttttgttct
2821 ttaaagtcag gtccaatttg taaaaacagc attgctttct gaaattaggg cccaattaat
2881 aatcagcaag aatttgatcg ttccagttcc cacttggagg cctttcatcc ctcgggtgtg
2941 ctatggatgg cttctaacaa aaactacaca tatgtattcc tgatcgccaa cctttccccc
3001 accagctaag gacatttccc agggttaata gggcctggtc cctgggagga aatttgaatg
3061 ggtccatttt gcccttccat agcctaatcc ctgggcattg ctttccactg aggttggggg
3121 ttggggtgta ctagttacac atcttcaaca gacccccctct agaaattttt cagatgcttc
3181 tgggagacac ccaaagggtg aagctattta tctgtagtaa actatttatc tgtgtttttg
3241 aaatattaaa ccctggatca gtcctttgat cagtataatt ttttaaagtt actttgtcag
3301 aggcacaaaa gggtttaaac tgattcataa taaatatctg tacttcttcg atcttcacct
3361 tttgtgctgt gattcttcag tttctaaacc agcactgtct gggtccctac aatgtatcag
3421 gaagagctga gaatggtaag gagactcttc taagtcttca tctcagagac cctgagttcc
3481 cactcagacc cactcagcca aatctcatgg aagaccaagg agggcagcac tgtttttgtt
3541 ttttgttttt tgtttttttt ttttgacact gtccaaaggt tttccatcct gtcctggaat
3601 cagagttgga agctgaggag cttcagcctc ttttatggtt taatggccac ctgttctctc
3661 ctgtgaaagg ctttgcaaag tcacattaag tttgcatgac ctgttatccc tggggcccta
3721 tttcatagag gctggcccta ttagtgattt ccaaaaacaa tatggaagtg ccttttgatg
3781 tcttacaata agagaagaag ccaatggaaa tgaaagagat tggcaaaggg gaaggatgat
3841 gccatgtaga tcctgtttga catttttatg gctgtatttg taaacttaaa cacaccagtg
3901 tctgttcttg atgcagttgc tatttaggat gagttaagtg cctggggagt ccctcaaaag
3961 gttaaaggga ttcccatcat tggaatctta tcaccagata ggcaagttta tgaccaaaca
4021 agagagtact ggctttatcc tctaacctca tattttctcc cacttggcaa gtcctttgtg
4081 gcatttattc atcagtcagg gtgtccgatt ggtcctagaa cttccaaagg ctgcttgtca
4141 tagaagccat tgcatctata aagcaacggc tcctgttaaa tggtatctcc tttctgaggc
4201 tcctactaaa agtcatttgt tacctaaact tatgtgctta acaggcaatg cttctcagac
4261 cacaaagcag aaagaagaag aaaagctcct gactaaatca gggctgggct tagacagagt
4321 tgatctgtag aatatcttta aaggagagat gtcaactttc tgcactattc ccagcctctg
4381 ctcctccctg tctaccctct cccctccctc tctccctcca cttcacccca caatcttgaa
4441 aaacttcctt tctcttctgt gaacatcatt ggccagatcc attttcagtg gtctggattt
4501 ctttttattt tcttttcaac ttgaaagaaa ctggacatta ggccactatg tgttgttact
4561 gccactagtg ttcaagtgcc tcttgttttc ccagagattt cctgggtctg ccagaggccc
4621 agacaggctc actcaagctc tttaactgaa aagcaacaag ccactccagg acaaggttca
4681 aaatggttac aacagcctct acctgtcgcc ccagggagaa aggggtagtg atacaagtct
4741 catagccaga gatggttttc cactccttct agatattccc aaaaagaggc tgagacagga
4801 ggttattttc aattttattt tggaattaaa tacttttttc cctttattac tgttgtagtc
4861 cctcacttgg atatacctct gttttcacga tagaaataag ggaggtctag agcttctatt
4921 ccttggccat tgtcaacgga gagctggcca agtcttcaca aacccttgca acattgcctg
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5041 acagcttgac tacacgtcat ttttaccaat gattttcagg tgacctgggc taagtcattt
5101 aaactgggtc tttataaaag taaaaggcca acatttaatt attttgcaaa gcaacctaag
5161 agctaaagat gtaatttttc ttgcaattgt aaatcttttg tgtctcctga agacttcccc
5221 taaaattagc tctgagtgaa aaatcaaaag agacaaaaga catcttcgaa tccatatttc
5281 aagcctggta gaattggctt ttctagcaga acctttccaa aagttttata ttgagattca
5341 taacaacacc aagaattgat tttgtagcca acattcattc aatactgtta tatcagagga
5401 gtaggagaga ggaaacattt gacttatctg gaaaagcaaa atgtacttaa gaataagaat
5461 aacatggtcc attcaccttt atgttataga tatgtctttg tgtaaatcat ttgttttgag
5521 ttttcaaaga atagcccatt gttcattctt gtgctgtaca atgaccactg ttattgttac
5581 tttgactttt cagagcacac ccttcctctg gtttttgtat atttattgat ggatcaataa
5641 taatgaggaa agcatgatat gtatattgct gagttgaaag cacttattgg 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 gctagcccgc agcgctcggc
  61 ttcctggtaa ttcttcacct cttttctcag ctccctgcag catgggtgct gggccctcct
 121 tgctgctcgc cgccctcctg ctgcttctct ccggcgacgg cgccgtgcgc tgcgacacac
 181 ctgccaactg cacctatctt gacctgctgg gcacctgggt cttccaggtg ggctccagcg
 241 gttcccagcg cgatgtcaac tgctcggtta tgggaccaca agaaaaaaaa gtagtggtgt
 301 accttcagaa gctggataca gcatatgatg accttggcaa ttctggccat ttcaccatca
 361 tttacaacca aggctttgag attgtgttga atgactacaa gtggtttgcc ttttttaagt
 421 ataaagaaga gggcagcaag gtgaccactt actgcaacga gacaatgact gggtgggtgc
 481 atgatgtgtt gggccggaac tgggcttgtt tcaccggaaa gaaggtggga actgcctctg
 541 agaatgtgta tgtcaacata gcacacctta agaattctca ggaaaagtat tctaataggc
 601 tctacaagta tgatcacaac tttgtgaaag ctatcaatgc cattcagaag tcttggactg
 661 caactacata catggaatat gagactctta ccctgggaga tatgattagg agaagtggtg
 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 tggaagaagc ttgcttcccc tacacaggca
1081 ctgattctcc atgcaaaatg aaggaagact gctttcgtta ttactcctct gagtaccact
1141 atgtaggagg tttctatgga ggctgcaatg aagccctgat gaagcttgag ttggtccatc
1201 atgggcccat ggcagttgct tttgaagtat atgatgactt cctccactac aaaaagggga
1261 tctaccacca cactggtcta agagaccctt tcaacccctt tgagctgact aatcatgctg
1321 ttctgcttgt gggctatggc actgactcag cctctgggat ggattactgg attgttaaaa
1381 acagctgggg caccggctgg ggtgagaatg gctacttccg gatccgcaga ggaactgatg
1441 agtgtgcaat tgagagcata gcagtggcag ccacaccaat tcctaaattg tagggtatgc
1501 cttccagtat ttcataatga tctgcatcag ttgtaaaggg gaattggtat attcacagac
1561 tgtagacttt cagcagcaat ctcagaagct tacaaataga tttccatgaa gatatttgtc
1621 ttcagaatta aaactgccct taatttttaat atacctttca atcggccact ggccattttt
1681 ttctaagtat tcaattaagt gggaattttc tggaagatgg tcagctatga agtaatagag
1741 tttgcttaat catttgtaat tcaaacatgc tatatttttt aaaatcaatg tgaaaacata
1801 gacttatttt taaattgtac caatcacaag aaaataatgg caataattat caaaacttttt
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 ctgggcgctc
  61 ggcttccact ccttcaggcg tcggcagcca ctagtcgtgg cgagaggggc ggggtggccg
 121 gggctggcgc tccacttggc ccccgctccc ggcccgcccc gccgccgcgg ccccccggat
 181 gagggtatat attcggagcg agcgcgggac gccgatgagt ggccgcgcgg aaggagctgg
 241 agacggtcgt agctgcggtc gcgccgagaa aggtttacag gtacatacat tacaccccta
 301 tttctacaaa gcttggctat tagagcatta tgaacattaa tgacctcaaa ctcacgttgt
 361 ccaaagctgg gcaagagcac ctactacgtt tctggaatga gcttgaagaa gcccaacagg
 421 tagaacttta tgcagagctc caggccatga actttgagga gctgaacttc tttttccaaa
 481 aggccattga aggttttaac cagtcttctc accaaaagaa tgtggatgca cgaatggaac
 541 ctgtgcctcg agaggtatta ggcagtgcta caagggatca agatcagctc caggcctggg
 601 aaagtgaagg acttttccag atttctcaga ataaagtagc agttcttctt ctagctggtg
 661 ggcaggggac aagactcggc gttgcatatc ctaaggggat gtatgatgtt ggtttgccat
 721 cccgtaagac actttttcag attcaagcag agcgtatcct gaagctacag caggttgctg
 781 aaaaatatta tggcaacaaa tgcattattc catggtatat aatgaccagt ggcagaacaa
 841 tggaatctac aaaggagttc ttcaccaagc acaagtactt tggtttaaaa aaagagaatg
 901 taatcttttt tcagcaagga atgctccccg ccatgagttt tgatgggaaa attattttgg
 961 aagagaagaa caaagtttct atggctccag atgggaatgg tggtctttat cgggcacttg
1021 cagcccagaa tattgtggag gatatggagc aaagaggcat ttggagcatt catgtctatt
1081 gtgttgacaa catattagta aaagtggcag acccacggtt cattggattt tgcattcaga
1141 aaggagcaga ctgtggagca aaggtggtag agaaaacgaa ccctacagaa ccagttggag
1201 tggtttgccg agtggatgga gtttaccagg tggtagaata tagtgagatt tccctggcaa
1261 cagctcaaaa acgaagctca gacggacgac tgctgttcaa tgcggggaac attgccaacc
1321 atttcttcac tgtaccattt ctgagagatg ttgtcaatgt ttatgaacct cagttgcagc
1381 accatgtggc tcaaaagaag attccttatg tggataccca aggacagtta attaagccag
1441 acaaacccaa tggaataaag 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 gaaagttatg tggcagataa agaattccat gcacctctaa
1801 tcatcgatga gaatggagtt catgagctgg tgaaaaatgg tatttgaacc agataccaag
1861 ttttgtttgc cacgatagga atagctttta ttttttgatag accaactgtg aacctacaag
1921 acgtcttgga caactgaagt ttaaatatcc acagggtttt attttgcttg ttgaactctt
1981 agagctattg caaacttccc aagatccaga tgactgaatt tcagatagca tttttatgat
2041 tcccaactca ttgaaggtct tatttatata attttttcca agccaaggag accattggcc
2101 atccaggaaa tttcgtacag ctgaaatata ggcaggatgt tcaacatcag tttacttgca
2161 gctggaagca tttgtttttg aagttgtaca tagtaataat atgtcattgt acatgttgaa
2221 aggtttctat ggtactaaaa gtttgtttta ttttatcaaa cattaagctt ttttaagaaa
2281 ataattgggc agtgaaataa atgtatcttc ttgtctctgg agtgtcaaaa aaaaaaaaaa
2341 aaaa
```

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 ggccgccggt gagtcggctg gagcgcatct ggtcctccgc gcggaaagcg
  61 ctgcttttgc ctggccgccc tagccgctgg ctcatccaag tggccttcgc cgctctcttg
 121 cgtcccaacc agagcgctgg ccacctcgcc gcccagctca cgccgcgccc gcgctcccag
 181 gctccgggtt ttcttaaatg ttttcttgga gccttaaaga tggagatgac agaaatgact
 241 ggtgtgtcgc tgaaacgtgg ggcactggtt gtcgaagata atgacagtgg agtcccagtt
 301 gaagagacaa aaaaacagaa gctgtcggaa tgcagtctaa ccaaaggtca agatgggcta
 361 cagaatgact ttctgtccat cagtgaagac gtgcctcggc ctcctgacac tgtcagtact
 421 gggaaaggtg gaaagaattc tgaggctcag ttggaagatg aggaagaaga ggaggaagat
 481 ggactttcag aggagtgcga ggaggaggaa tcagagagtt ttgcagacat gatgaagcat
 541 ggactcactg aggctgacgt aggcatcacc aagtttgtga gttctcatca agggttctcg
 601 ggaatcttaa aagaaagata ctccgacttc gttgttcatg 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 aagaaataca ttgtagccta ccacgcagct gggaaaaagg ctttggcaaa tccaagaaaa
 961 cattcttggc caaaatctag gggaagttac tgccacttcg tactatataa ggaaaacaaa
1021 gacaccatgg atgctattaa tgtactctcc aaatacttaa gagtcaagcc aaatatattc
1081 tcctacatgg gaaccaaaga taaaagggct ataacagttc aagaaattgc tgttctcaaa
1141 ataactgcac aaagacttgc ccacctgaat aagtgcttga tgaactttaa gctagggaat
1201 ttcagctatc aaaaaaaccc actgaaattg ggagagcttc aaggaaacca cttcactgtt
1261 gttctcagaa atataacagg aactgatgac caagtacagc aagctatgaa ctctctcaag
1321 gagattggat ttattaacta ctatggaatg caaagatttg gaaccacagc tgtccctacg
1381 tatcaggttg gaagagctat actacaaaat tcctggacag aagtcatgga tttaatattg
1441 aaacccccgct ctggagctga aaagggctac ttggttaaat gcagagaaga atgggcaaag
1501 accaaagacc caactgctgc cctcagaaaa ctacctgtca aaaggtgtgt ggaagggcag
1561 ctgcttcgag gactttcaaa atatggaatg aagaatatag tctctgcatt tggcataata
1621 cccagaaata atcgcttaat gtatattcat agctaccaaa gctatgtgtg gaataacatg
1681 gtaagcaaga ggatagaaga ctatggacta aaacctgttc caggggacct cgttctcaaa
1741 ggagccacag ccacctatat tgaggaagat gatgttaata attactctat ccatgatgtg
1801 gtaatgccct tgcctggttt cgatgttatc tacccaaagc ataaaattca agaagcctac
1861 agggaaatgc tcacagctga caatcttgat attgacaaca tgagacacaa aattcgagat
1921 tattccttgt caggggccta ccgaaagatc attattcgtc ctcagaatgt tagctgggaa
1981 gtcgttgcat atgatgatcc caaaattcca cttttcaaca cagatgtgga caacctagaa
2041 gggaagacac caccagtttt tgcttctgaa ggcaaataca gggctctgaa aatggatttt
2101 tctctacccc cttctactta cgccaccatg gccattcgag aagtgctaaa aatggatacc
2161 agtatcaaga accagacgca gctgaataca acctggcttc gctgagcagt accttgtcca
2221 cagattagaa aacgtacaca agtgtttgct tcctggctcc ctgtgcattt ttgtcttagt
2281 tcagactcat atatggattt caaatctttg taataaaaat tatttgtatt tttaagtttt
2341 tattagctta aagaaataat ttgcaatatt tgtacatgta cacaaatcct gaggttctta
2401 attttagctc agaatataaa 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 cacccacaaa tataaataca gtactcatgc tgactgaaat aataagacat ctacaaattt
```

Figure 6-29

```
2701 ataaacaaaa agtgattgtc attatcctgc ttatgtacta gattcaggca agcattatag
2761 acttttggt tgcggtggct tttgcattta tattatcaat gccttgcagg aacgttgcat
2821 tgataggccc attttatttt tttatttttt ttttcgagac aggatctcac tctgtagcac
2881 aggctggatt gcagtgcaat cctgcaattc tcaatcttgc actgcagcct cgacctccca
2941 ggctccagtg actctcccac ctcagcctcc taagtagctg ggagtacagg cgcgcaccac
3001 cacgcctagc tgatttttgt atttttttgt agagacgggg gtttggccat gttgccgagg
3061 ctaactcctg ggattacagg catgagctgt gctggccggg ttttttttte ttgatgtaaa
3121 cgtgtacagc tgttttatta gttaaggtct aatttttact ctaggtgcct tttatgttca
3181 gaactctttc cactggactg gtatttgctc aaaaataaat aatggtagag aagaaaacta
3241 taaaaatgga caaggctttc ttctatcagt agcgtttacc ctttgtcacc agtggctttg
3301 gtatttccat gtctggcatt gcataaactt 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 atggaatgtt
 181 tccacatatt ataccaccaa catgagaaaa aaatgatcat tgtttatttg aagcttgatg
 241 atattctaac gctgcctttt ctcttctcat tttagagaaa aatgagcagg cggaattgtt
 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 agtggtgggt ttgatctttt tatttagaaa cccacaaaat
 841 cagaaacaca gtacaaataa aacagaaatc aaactataag ttgactttta gttcctaaaa
 901 agaaacatat ttcaaaagca atggaatcta gaattcttat aacatgaata acaaaatgta
 961 cagcaagcct atgtagttca attaatatat aaggaaaagg aaggtctttc ttcatgatac
1021 aagcattata aagtttttac tgtagtagtc aattaatgga tatttccttg ttaataaaat
1081 tttgtgtcat aatttacaaa ttagttcttt aaaaattgtt gttatatgaa ttgtgtttct
1141 agcatgaatg ttctatagag tactctaaat aacttgaatt tatagacaaa tgctactcac
1201 agtacaatca attgtattat accatgagaa aatcaaaaag gtgttcttca gagacatttt
1261 atctataaaa ttttcctact attatgttca ttaacaaact tctttatcac atgtatcttc
1321 tacatgtaaa acatttctga tgatttttta acaaaaaata tatgaatttc ttcatttgct
1381 cttgcatcta cattgctata aggatataaa atgtggtttc tatattttga gatgtttttt
1441 ccttacaatg tgaactcatc gtgatcttgg aaatcaataa agtcaaatat caactaaa
```

Figure 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 cagggtccct gaagagggaa gacacgcgga aacaggcttg
  61 cacccagaca cgacaccatg catctcctcg gcccctggct cctgctcctg gttctagaat
 121 acttggcttt ctctgactca agtaaatggg tttttgagca ccctgaaacc ctctacgcct
 181 gggagggggc ctgcgtctgg atcccctgca cctacagagc cctagatggt gacctggaaa
 241 gcttcatcct gttccacaat cctgagtata acaagaacac ctcgaagttt gatgggacaa
 301 gactctatga aagcacaaag gatgggaagg ttccttctga gcagaaaagg gtgcaattcc
 361 tgggagacaa gaataagaac tgcacactga gtatccaccc ggtgcacctc aatgacagtg
 421 gtcagctggg gctgaggatg gagtccaaga ctgagaaatg gatggaacga atacacctca
 481 atgtctctga aaggcctttt ccacctcata tccagctccc tccagaaatt caagagtccc
 541 aggaagtcac tctgacctgc ttgctgaatt tctcctgcta tgggtatccg atccaattgc
 601 agtggctcct agagggggtt ccaatgaggc aggctgctgt cacctcgacc tccttgacca
 661 tcaagtctgt cttcacccgg agcgagctca agttctcccc acagtggagt caccatggga
 721 agattgtgac ctgccagctt caggatgcag atgggaagtt cctctccaat gacacggtgc
 781 agctgaacgt gaagcacacc ccgaagttgg agatcaaggt cactcccagt gatgccatag
 841 tgagggaggg ggactctgtg accatgacct gcgaggtcag cagcagcaac ccggagtaca
 901 cgacggtatc ctggctcaag gatgggacct cgctgaagaa gcagaataca ttcacgctaa
 961 acctgcgcga agtgaccaag gaccagagtg cgaagtactg ctgtcaggtc tccaatgacg
1021 tgggcccggg aaggtcggaa gaagtgttcc tgcaagtgca gtatgccccg gaaccttcca
1081 cggttcagat cctccactca ccggctgtgg agggaagtca agtcgagttt ctttgcatgt
1141 cactggccaa tcctcttcca acaaattaca cgtggtacca caatgggaaa gaaatgcagg
1201 gaaggacaga ggagaaagtc cacatcccaa agatcctccc ctggcacgct gggacttatt
1261 cctgtgtggc agaaaacatt cttggtactg cacagagggg cccgggagct gagctggatg
1321 tccagtatcc tcccaagaag gtgaccacag tgattcaaaa ccccatgccg attcgagaag
1381 gagacacagt gaccctttcc tgtaactaca attccagtaa ccccagtgtt acccggtatg
1441 aatggaaacc ccatggcgcc tgggaggagc catcgcttgg ggtgctgaag atccaaaacg
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1561 cccctgtcgc cctgaatgtc cagtatgccc cccgagacgt gagggtccgg aaaatcaagc
1621 ccctttccga gattcactct ggaaactcgg tcagcctcca atgtgacttc tcaagcagcc
1681 accccaaaga agtccagttc ttctgggaga aaaatggcag gcttctgggg aaagaaagcc
1741 agctgaattt tgactccatc tccccagaag atgctgggag ttacagctgc tgggtgaaca
1801 actccatagg acagacagcg tccaaggcct cgacacttga agtgctgtat gcacccagga
1861 ggctgcgtgt gtccatgagc ccgggggacc aagtgatgga ggggaagagt gcaaccctga
1921 cctgtgagag cgacgccaac cctcccgtct cccactacac ctggtttgac tggaataacc
1981 aaagcctccc ctaccacagc cagaagctga cattggagcc ggtgaaggtc cagcactcgg
2041 gtgcctactg gtgccagggg accaacagtg tgggcaaggg ccgttcgcct ctcagcaccc
2101 tcaccgtcta ctatagcccg gagaccatcg gcaggcgagt ggctgtggga ctcgggtcct
2161 gcctcgccat cctcatcctg gcaatctgtg ggctcaagct ccagcgacgt tggaagagga
2221 cacagagcca gcaggggctt caggagaatt ccagcggcca gagcttcttt gtgaggaata
2281 aaaaggttag aagggccccc ctctctgaag gcccccactc cctgggatgc tacaatccaa
2341 tgatggaaga tggcattagc tacaccaccc tgcgctttcc cgagatgaac ataccacgaa
2401 ctggagatgc agagtcctca gagatgcaga gacctccccc ggactgcgat gacacggtca
2461 cttattcagc attgcacaag cgccaagtgg gcgactatga gaacgtcatt ccagattttc
2521 cagaagatga ggggattcat tactcagagc tgatccagtt tggggtcggg gagcggcctc
2581 aggcacaaga aaatgtggac tatgtgatcc tcaaacattg acactggatg ggctgcagca
2641 gaggcactgg gggcagcggg ggccagggaa gtccccgagt ttccccagac accgccacat
```

Figure 6-32

```
2701 ggctcctcc tgcgcgcatg tgcgcacaca cacacacaca cgcacacaca cacacacaca
2761 ctcactgcgg agaaccttgt gcctggctca gagccagtct ttttggtgag ggtaacccca
2821 aaccccaaa actcctgccc ctgttctctt ccactctcct tgctacccag aaatccatct
2881 aaatacctgc cctgacatgc acacctcccc ctgcccccac cacggccact ggccatctcc
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3121 ggccggctt ctcctttgga 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 tacaagcggt
  61 cctcccggcc accgtactgt tccgctccca gaagccccgg gcggcggaag tcgtcactct
 121 taagaaggga cggggcccca cgctgcgcac ccgcgggttt gctatggcga tgagcagcgg
 181 cggcagtggt ggcggcgtcc cggagcagga ggattccgtg ctgttccggc gcggcacagg
 241 ccagagcgat gattctgaca tttgggatga tacagcactg ataaaagcat atgataaagc
 301 tgtggcttca tttaagcatg ctctaaagaa tggtgacatt tgtgaaactt cgggtaaacc
 361 aaaaaccaca cctaaaagaa aacctgctaa gaagaataaa agccaaaaga agaatactgc
 421 agcttcctta caacagtgga aagttgggga caaatgttct gccatttggt cagaagacgg
 481 ttgcatttac ccagctacca ttgcttcaat tgattttaag agagaaacct gtgttgtggt
 541 ttacactgga tatggaaata gagaggagca aaatctgtcc gatctacttt ccccaatctg
 601 tgaagtagct aataatatag aacagaatgc tcaagagaat gaaaatgaaa gccaagtttc
 661 aacagatgaa agtgagaact ccaggtctcc tggaaataaa tcagataaca tcaagcccaa
 721 atctgctcca tggaactctt ttctccctcc accacccccc atgccagggc caagactggg
 781 accaggaaag ccaggtctaa aattcaatgg cccaccaccg ccaccgccac caccaccacc
 841 ccacttacta tcatgctggc tgcctccatt tccttctgga ccaccaataa ttcccccacc
 901 acctcccata tgtccagatt ctcttgatga tgctgatgct ttgggaagta tgttaatttc
 961 atggtacatg agtggctatc atactggcta ttatatgggt ttcagacaaa atcaaaaaga
1021 aggaaggtgc tcacattcct taaattaagg agaaatgctg gcatagagca gcactaaatg
1081 acaccactaa agaaacgatc agacagatct ggaatgtgaa gcgttataga agataactgg
1141 cctcatttct tcaaaatatc aagtgttggg aaagaaaaaa ggaagtggaa tgggtaactc
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1261 tgaaaaacca tctgtaaaag actggggtgg gggtgggagg ccagcacggt ggtgaggcag
1321 ttgagaaaat ttgaatgtgg attagatttt gaatgatatt ggataattat tggtaatttt
1381 atggcctgtg agaagggtgt tgtagtttat aaaagactgt cttaatttgc atacttaagc
1441 atttaggaat gaagtgttag agtgtcttaa aatgtttcaa atggtttaac aaaatgtatg
1501 tgaggcgtat gtggcaaaat gttacagaat ctaactggtg gacatggctg ttcattgtac
1561 tgttttttc 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

```
   1 aagttgcttt tgtccaaaca tccgggcttc tccttttttgt gttccggccg atcccacctc
  61 tcctcgaccc tggacgtcta ccttccggag gcccacatct tgcccactcc gcgcgcgggg
 121 ctagcgcggg tttcagcgac gggagccctc aagggacatg gcaactacag cggcgccggc
 181 gggcggcgcc cgaaatggag ctggcccgga 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 cctccagcgc
 481 cttcagcttg tacgccaaca tcgacatcct cagaccctac tttgatgtgg agcctgctca
 541 ggtgcgaagc aggctcctgg agtccatgat ccctatcaag atggtcaact tcccccagaa
 601 aattgcaggt gaactctatg gacctctcat gctggtcttc actctggttg ctatcctact
 661 ccatgggatg aagacgtctg acactattat ccgggagggc accctgatgg gcacagccat
 721 tggcacctgc ttcggctact 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 atcccgccca tccagagggt ccccagagac atccctgcca tgctccctgc
1141 tgctcggctt cccaccaccg tcctcaacgc cacagccaaa gctgttgcgg tgaccctgca
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1261 ggaagactat taaaggacag tcctgatgac atgtttcgta gatggggttt gcagctgcca
1321 ctgagctgta gctgcgtaag tacctccttg atgcctgtcg gcacttctga aaggcacaag
1381 gccaagaact cctggccagg actgcaaggc tctgcagcca atgcagaaaa tgggtcagct
1441 cctttgagaa cccctcccca cctacccctt ccttcctctt tatctctccc acattgtctt
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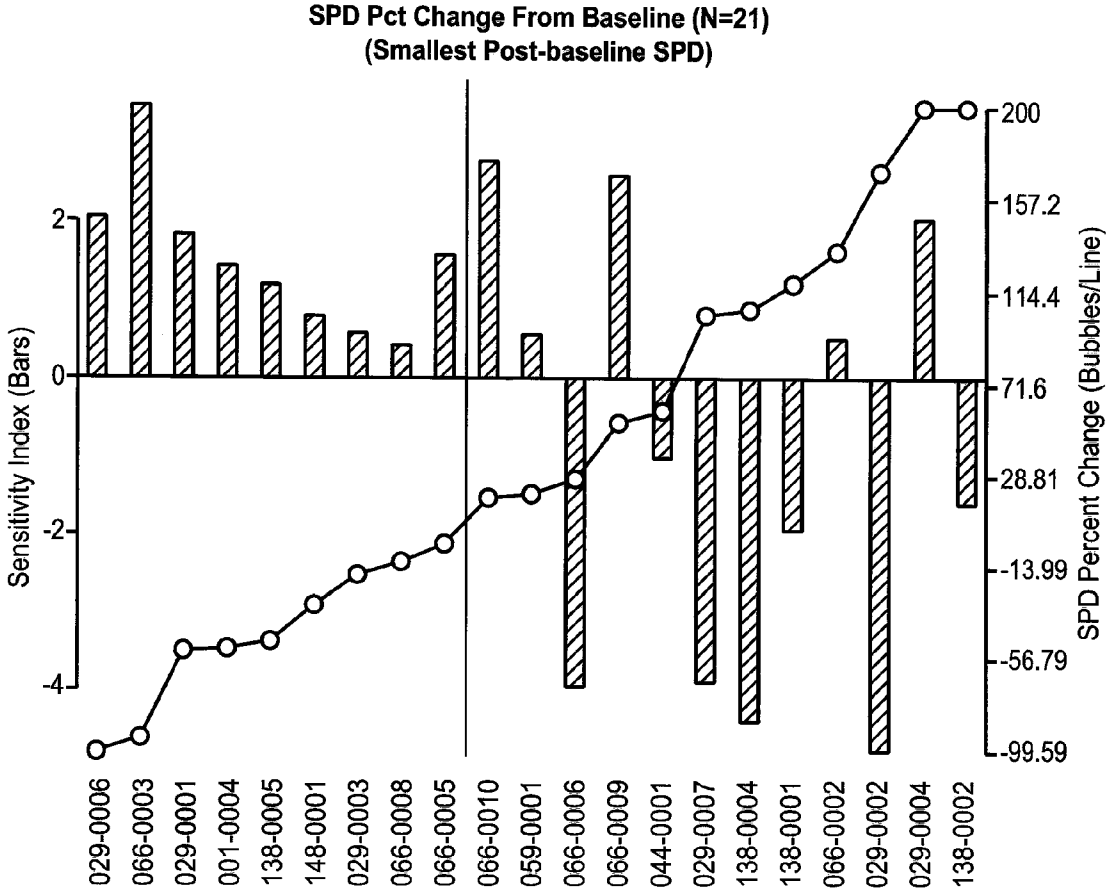
1561 aaaccaaaaa aa
```

Figure 6-35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(Smallest Post-baseline SPD)
Sensitivity Index (Bars)
SPD Percent Change (Bubbles/Line)
2
0
-2
-4
200
157.2
114.4
71.6
28.81
-13.99
-56.79
-99.59
029-0006
066-0003
029-0001
001-0004
138-0005
148-0001
029-0003
066-0008
066-0005
066-0010
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066-0006
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138-0001
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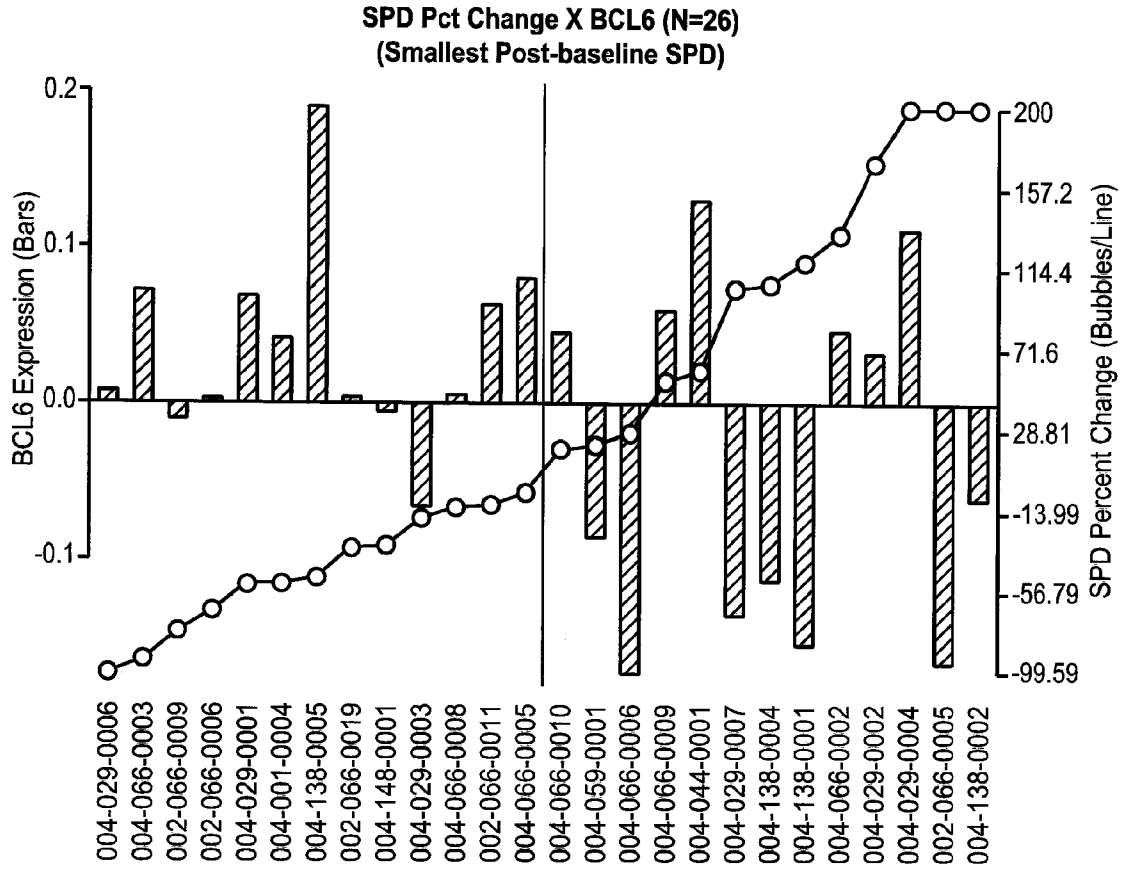
029-0002
029-0004
138-0002

FIG. 7


SPD Pct Change X BCL6 (N=26)
(Smallest Post-baseline SPD)
BCL6 Expression (Bars)
SPD Percent Change (Bubbles/Line)
0.2
0.1
0.0
-0.1
200
157.2
114.4
71.6
28.81
-13.99
-56.79
-99.59
004-029-0006
004-066-0003
002-066-0009
002-066-0006
004-029-0001
004-001-0004
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002-066-0019
004-148-0001
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004-066-0008
002-066-0011
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004-066-0010
004-059-0001
004-066-0006
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004-044-0001
004-029-0007
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004-029-0002
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004-138-0002

FIG. 8

SEQUENCE LISTING

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DORNAN, David
BURINGTON, Bruce

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

<130> 146392001740

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<141> 2008-11-07

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35 40 45
Ala Arg Val Ile Pro Asn Ala Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Arg Phe Thr Leu Ser Val Asp Asn Ser Lys Asn Thr Ala Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Ile Tyr Trp Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110
Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
115 120 125
Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
130 135 140
Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
145 150 155 160
Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
165 170 175
Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
180 185 190
Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
195 200 205
Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
210 215 220
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe

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225                 230                 235                 240
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
                245                 250                 255
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
            260                 265                 270
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
        275                 280                 285
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
    290                 295                 300
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305                 310                 315                 320
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
                325                 330                 335
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
            340                 345                 350
Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
        355                 360                 365
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
    370                 375                 380
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
385                 390                 395                 400
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
                405                 410                 415
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
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            20                  25                  30
Asn Gly Asn Thr Phe Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
        35                  40                  45
Pro Lys Leu Leu Ile Tyr Thr Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65                  70                  75                  80
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys Ser Gln Thr
                85                  90                  95
Thr His Val Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
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Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
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<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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