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Methods for the identification, assessment, and treatment of patients with proteasome inhibition therapy

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(54) Title: METHODS FOR THE IDENTIFICATION, ASSESSMENT, AND TREATMENT OF PATIENTS WITH PROTEASOME INHIBITION THERAPY

(57) Abstract: The present invention is directed to the identification of markers that can be used to determine whether patients with cancer are clinically responsive or non-responsive to a therapeutic regimen prior to treatment. In particular, the present invention is directed to the use of certain combinations of markers, wherein the expression of the markers correlates with responsiveness or non-responsiveness to a therapeutic regimen comprising proteasome inhibition. Thus, by examining the expression levels of individual markers and those comprising a marker set, it is possible to determine whether a therapeutic agent, or combination of agents, will be most likely to reduce the growth rate of tumors in a clinical setting.

METHODS FOR THE IDENTIFICATION, ASSESSMENT, AND TREATMENT OF PATIENTS WITH PROTEASOME INHIBITION THERAPY

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Number 60/431,514, filed December 6, 2002, the contents of which are incorporated herein by this reference.

BACKGROUND OF THE INVENTION

[0002] Proteasome inhibition represents an important recently developed strategy in cancer treatment. The proteasome is a multi-enzyme complex present in all cells which plays a role in degradation of proteins involved in regulation of the cell cycle. For example, King *et al.*, demonstrated that the ubiquitin-proteasome pathway plays an essential role in regulating cell cycle, neoplastic growth and metastasis. A number of key regulatory proteins, including p53, cyclins, and the cyclin-dependent kinases p21 and $p27^{KIP1}$, are temporally degraded during the cell cycle by the ubiquitin-proteasome pathway. The ordered degradation of these proteins is required for the cell to progress through the cell cycle and to undergo mitosis. See, *e.g., Science* 274:1652-1659 (1996). Furthermore, the ubiquitin-proteasome pathway is required for transcriptional regulation. Palombella *et al.*, teach that the activation of the transcription factor NF-kB is regulated by proteasome-mediated degradation of the inhibitor protein IkB. See International Patent Application Publication No. WO 95/25533. In turn, NF-kB plays a central role in the regulation of genes involved in the immune and inflammatory responses. For example, Read *et al.* demonstrated that the ubiquitin-proteasome pathway is required for expression of cell adhesion molecules, such as E-selectin, ICAM-1, and VCAM-1. See *Immunity* 2:493-506 (1995). Additional findings further support the role for proteasome inhibition in cancer therapy, as Zetter found that cell adhesion molecules are involved in tumor metastasis and angiogenesis *in vivo*, by directing the adhesion and extravastation of tumor cells to and from the vasculature to distant tissue sites within the body. See, *e.g., Seminars in Cancer Biology* 4:219-229 (1993). Moreover, Beg and Baltimore, found that NF-kB is an anti-apoptotic factor, and inhibition of NF-kB activation makes cells more sensitive to environmental stress and cytotoxic agents. See *Science* 274:782 (1996).

[0003] Adams *et al.* have described peptide boronic ester and acid compounds useful as proteasome inhibitors. See, *e.g.,* U.S. Patent No. 5,780,454 (1998), U.S. Patent No. 6,066,730 (2000), and U.S. Patent No. 6,083,903 (2000). They describe the use of the disclosed boronic ester and boronic acid compounds to reduce the rate of muscle protein degradation, to reduce the activity of NF-kB in a cell, to reduce the rate of degradation of p53 protein in a cell, to inhibit cyclin degradation in a cell, to inhibit the growth of a cancer cell, and to inhibit NF-kB dependent cell adhesion. Adams *et al.* have described one of the compounds, N-pyrazinecarbonyl-L-phenylalanine-L-leucineboronic acid (PS-341, now know as bortezomib) as having demonstrated antitumor activity in human tumor xenograft models. This particular compound has recently received approval for treatment of patients having relapsed refractory multiple myeloma, and is presently undergoing clinical trials in additional indications, including additional hematological cancers as well as solid tumors.

[0004] Because the proteasome plays a pervasive role in normal physiology as well as pathology, it is important to optimize (e.g., avoid excessive) proteasome inhibition when using proteasome inhibitors as therapeutic agents. Moreover, one of the continued problems with therapy in cancer patients is individual differences in response to therapies. With the narrow therapeutic index and the toxic potential of many available cancer therapies, this potentially contributes to many patients undergoing unnecessary ineffective and even harmful therapy regimens. If a designed therapy could be optimized to treat individual patients, such situations could be reduced or even eliminated. Accordingly, there is a need to identify particular cancer patients against which proteasome inhibitors are particularly effective, either alone or in combination with other chemotherapies. Also, there is a need to identify particular patients who respond well to treatment with a proteasome inhibitor (responders) versus those patient who do not respond to proteasome treatment (non-responders). It would therefore be beneficial to provide for the diagnosis, staging, prognosis, and monitoring of cancer patients, including, e.g., hematological cancer patients (e.g., multiple myeloma, leukemias, lymphoma, etc) as well as solid tumor cancer patients, who would benefit from proteasome inhibition therapies; or to indicate a predisposition of such patients to such preventative measures. The present invention is directed towards these needs.

DESCRIPTION OF THE INVENTION

[0005] The present invention is directed to the methods of identifying or selecting a cancer patient who is responsive to a therapeutic regimen comprising proteasome inhibition therapy. Additionally provided are methods of identifying a patient who is non-responsive to such a therapeutic regimen. These methods typically include the determining the level of expression of one or more predictive markers in a patient's tumor (e.g., a patient's cancer cells), and identifying whether expression in the sample includes a pattern or profile of expression of a selected predictive marker or marker set which correlates with response or non-response to proteasome inhibition therapy.

[0006] Additionally provided methods include therapeutic methods which further include the step of beginning, continuing, or commencing, or stopping, discontinuing or halting a proteasome inhibition therapy accordingly where a patient's predictive marker profile indicates that the patient would respond or not respond to the therapeutic regimen. In another embodiment, methods are provided for analysis of a patient not yet being treated with a proteasome inhibition therapy and identification and prediction that the patient would not be a responder to the therapeutic agent and such patient should not be treated with the proteasome inhibition therapy when the patient's marker profile indicates that the patient is a non-responder. Thus, the provided methods of the invention can eliminate ineffective or inappropriate use of proteasome inhibition therapy regimens.

[0007] The present invention is also directed to methods of treating a cancer patient, with a proteasome inhibition regimen, (e.g., a proteasome inhibitor agent, alone, or in combination with an additional agent such as a chemotherapeutic agent) which includes the step of selecting a patient whose predictive marker profile indicates that the patient will respond to the therapeutic agent, and treating the patient with the proteasome inhibition therapy regimen.

[0008] The present methods and compositions are designed for use in diagnostics and therapeutics for a patient suffering from cancer. The cancer can be of the liquid or solid tumor type. Liquid tumors include tumors of hematological origin, including, e.g., myelomas (e.g., multiple myeloma), leukemias (e.g., Waldenstrom's syndrome, chronic lymphocytic leukemia, other leukemias), and lymphomas (e.g., B-cell lymphomas, non-Hodgkins lymphoma). Solid tumors can originate in organs, and include cancers such as lung, breast, prostate, ovary, colon, kidney, and liver.

[0009] Therapeutic agents for use in the methods of the invention include a new class of therapeutic agents known as proteosome inhibitors. One example of a proteosome inhibitor that was recently approved for treatment of relapsed refractory multiple myeloma patients and is presently being tested in clinical trials for additional indications is bortezomib. Other examples of proteosome inhibitors are known in the art and are described in further detail herein. Proteasome inhibition therapy regimens can also include additional therapeutic agents such as chemotherapeutic agents. Some examples of traditional chemotherapeutic agents are set forth in Table A. Alternatively or in combination with these chemotherapeutic agents, newer classes of chemotherapeutic agents can also be used in proteasome inhibition therapy.

[0010] One embodiment of the invention provides methods for determining a proteasome inhibition-based regimen for treating a tumor in a patient. Such methods comprise measuring the level of expression of at least one predictive marker in the patient's tumor and determining a proteasome inhibition based regimen for treating the tumor based on the expression level of the predictive marker or markers, as relevant. A significant expression level of predictive marker or markers in the patient sample can be an indication that the patient is a responsive patient and would benefit from proteasome inhibition therapy when the predictive marker or marker set provided herein indicate such responsiveness. Additionally, a significant expression level of a predictive marker or markers in a patient can be an indication that the patient is a non-responsive patient and would not benefit from proteasome inhibition therapy when the marker or markers provided herein indicate such non-responsiveness.

[0011] The invention further provides methods for determining whether a patient will be responsive to a proteasome inhibition-based regimen for treating a tumor. Such methods comprise measuring the level of expression of at least one predictive marker in the patient's tumor and determining a proteasome inhibition based regimen for treating the tumor based on the expression level of the predictive marker or marker set. A significant expression level of a predictive marker in the patient sample is an indication that the patient is a responsive patient and would benefit from proteasome inhibition therapy. A significant expression level of a predictive marker set in the patient is an indication that the patient is a responsive patient and would benefit from proteasome inhibition therapy when the marker or markers provided herein indicate such responsiveness. Selected predictive markers for

use in the methods comprise responsive predictive markers as indicated in Table 1, Table 2, and Table 3.

[0012] Still further, the invention further provides methods for determining whether a patient will be non-responsive to a proteasome inhibition-based regimen for treating a tumor. Such methods comprise measuring the level of expression of at least one predictive marker in the patient's tumor and determining a proteasome inhibition based regimen for treating the tumor based on the expression level of the predictive marker or marker set. A significant expression level of a predictive marker in the patient sample is an indication that the patient is a non-responsive patient and would not benefit from proteasome inhibition therapy. A significant expression level of a predictive marker set in the patient is an indication that the patient is a non-responsive patient and would not benefit from proteasome inhibition therapy when the selected marker or marker set provided herein indicate such non-responsiveness. Selected predictive markers for use in the methods comprise non-responsive predictive markers as indicated in Table 1 Table 2 and Table 3.

[0013] Another embodiment of the invention provides methods for treating a tumor in a patient with proteasome inhibition therapy. Such therapeutic methods comprise measuring the level of expression of at least one predictive marker in a patient's tumor; determining whether a proteasome inhibition based regimen for treating the tumor is appropriate based on the expression level of the predictive marker or markers, and treating a patient with a proteasome inhibition therapy when the patient's expression level indicates a responsive patient. A significant expression level of predictive marker in the patient sample is an indication that the patient is a responsive patient and would benefit from proteasome inhibition therapy when the predictive marker or marker set provided herein indicate the patient is a responsive patient.

[0014] In certain aspects, the level of expression of predictive marker in the patient's tumor can be measured by isolating a sample of the tumor and performing analysis on the isolated sample, or a portion thereof. In another aspect, the level of expression of predictive marker in the patient's tumor can be measured using in vivo imaging techniques.

[0015] In certain aspects, determining the level of expression comprises detection of mRNA. Such detection can be carried out by any relevant method, including e.g., PCR, northern, nucleotide array detection, in vivo imaging using nucleic acid probes. In other aspects, determining the level of expression of the predictive marker comprises detection of protein. Such detection can be carried out using any relevant method for protein detection,

including w.g., ELISA, western blot, immunoassay, protein array detection, in vivo imaging using peptide probes.

[0016] Determining the level of expression of a predictive marker can be compared to a predetermined standard control level of expression in order to evaluate if expression of a marker or marker set is significant and make an assessment for determining whether the patient is responsive or non-responsive. Additionally, determining the level of expression of a predictive marker can be compared to an internal control marker level of expression which is measured at the same time as the predictive marker in order to make an assessment for determining whether the patient is responsive or non-responsive. The level of expression may be determined as significantly over-expressed in certain aspects. The level of expression may be under-expressed in other aspects. In still other aspects, the level of expression is determined against a pre-determined standard as determined by the methods provided herein.

[0017] Methods of the invention can use at least one of the predictive markers set forth in any one of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7. Additionally, the methods provided can use two, three, four, five, six, or more markers to form a predictive marker set. For example, marker sets selected from the markers in Table 1, Table 2 and/or Table 3 can be generated using the methods provided herein and can comprise between two, and all of the markers set forth in Table 1, Table 2 or Table 3 and each and every combination in between (e.g., four selected markers, 16 selected markers, 74 selected markers, etc.). In one embodiment, the markers comprise those set forth in Table 4, Table 5 or Table 6.

[0018] Methods of the invention further provide the ability to construct marker sets from the individual predictive markers set forth in Table 1 Table 2 and Table 3 using the methods described in further detail herein. In a further aspect, more than one marker set can be used in combination for the diagnostic, prognostic and treatment methods provided.

[0019] The methods of the invention can be performed such that determination of the level of expression of a predictive marker is measured prior to tumor therapy in order to identify whether the patient will be responsive to a proteasome inhibition therapy.

[0020] In addition, the methods of the invention can be performed concurrently with ongoing tumor therapy to determine if the patient is either responding to present proteasome inhibition therapy or will respond to additional therapy comprising proteasome inhibition therapy.

[0021] Still further, the methods of the invention can be performed after tumor therapy has been carried out in order to assess whether the patient will be responsive to future course of proteasome inhibition therapy.

[0022] Whether the methods are performed during ongoing tumor therapy or after a course of tumor therapy, the tumor therapy can comprise proteasome inhibition therapy or alternative forms of cancer therapy. The methods provided are designed to determine if the patient will benefit from additional or future proteasome inhibition therapy, and can include such proteasome inhibition therapy alone or in combination with additional therapeutic agents.

[0023] The invention also relates to various reagents and kits for diagnosing, staging, prognosing, monitoring and treating a cancer patient.

[0024] Provided are marker sets and methods for identification of marker sets comprising at least two isolated predictive markers set forth in Table 1, Table 2 and Table 3. The marker sets comprise reagents for detection of the relevant predictive markers set forth in Table 1, Table 2 and Table 3. Such reagents include nucleic acid probes, primers, antibodies, antibody derivatives, antibody fragments, and peptide probes.

[0025] Further provided are kits for use in determining a proteasome inhibition based regimen for treating a tumor in a patient. The kits of the invention include reagents for assessing predictive markers (e.g., at least one predictive marker) and predictive marker sets (e.g., at least two, three, four or more markers selected from Table 1, Table 2 and Table 3), as well as instructions for use in accordance with the methods provided herein. In certain aspects, the kits provided contain nucleic acid probes for assessment of predictive markers. In still other aspects, the kits provided contain antibody, antibody derivative antibody fragment, or peptide reagents for assessment of predictive markers.

[0026] According to the invention, the markers and marker sets are selected such that the positive predictive value of the methods of the invention is at least about 10%, preferably about 25%, more preferably about 50% and most preferably about 75%, 80%, 85%, or 90% or greater. Also preferred for use in the methods of the invention are markers that are differentially expressed in tumors, as compared to normal cells, by at least one-and-a-half-fold and preferably at least two-fold in at least about 20%, more preferably about 50%, and most preferably about 75% or more of any of the following conditions: partial responders, complete responders, minimal responders, and non-responders to proteasome inhibition therapy.

[0027] The present invention further provides previously unknown or unrecognized targets for the development of anti-cancer agents, e.g., chemotherapeutic compounds. The predictive markers and marker sets provided by the present invention also provide new targets either alone or in combination, which can be used for the development of novel therapeutics for cancers. Thus, nucleic acids and proteins represented by each of the markers provided can be used as targets in developing treatments (either single agent or multiple agent) for cancers, including e.g, hematological malignancies or solid tumor malignancies.

[0028] Thus, additionally provided are methods for use of the identified predictive markers, as well as the corresponding nucleic acid and polypeptides for screening methods for identification of novel compounds for use as anti-cancer therapeutics. Such newly identified compounds can be useful alone, or in combination with proteasome inhibition therapy as a complementary therapeutic.

[0029] The present invention is based, in part, on the identification of individual markers and marker sets that can be used to determine whether a tumor may be effectively treated by treatment with a proteasome inhibition therapy. For example, the compositions and methods provided herein can be used to determine whether a patient will be responsive or non-responsive to a proteasome inhibition therapeutic agent. Based on these identifications, the present invention provides, without limitation: 1) methods and compositions for determining whether a proteasome inhibition therapy will or will not be effective in stopping or slowing tumor growth; 2) methods and compositions for monitoring the effectiveness of a proteasome inhibition therapy (a proteasome inhibitor agent or a combination of agents) used for the treatment of tumors; 3) methods and compositions for identifying combinations of therapeutic agents for use in treating tumors; 4) methods and compositions for identifying specific therapeutic agents and combinations of therapeutic agents that are effective for the treatment of tumors in specific patients; 5) methods and compositions for identifying new targets for therapeutic agents for the treatment of tumors; and 6) methods and compositions for identifying new therapeutic agents for the treatment of tumors.

Definitions

[0030] Unless otherwise defined, all 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. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described herein. The content of all GenBank or RefSeq database records cited throughout this application (including the Tables) are also hereby incorporated by reference. In the case of conflict, the present specification, including definitions, will control.

[0031] The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.* to at least one) of the grammatical object of the article. By way of example, "an element" means at least one element and can include more than one element.

[0032] A "marker" is a naturally-occurring polymer corresponding to at least one of the nucleic acids or proteins associated with Affymetrix probe set identifiers listed in any one of Table 1, Table 2 or Table 3 For example, markers include, without limitation, sense and anti-sense strands of genomic DNA (*i.e.* including any introns occurring therein), RNA generated by transcription of genomic DNA (*i.e.* prior to splicing), RNA generated by splicing of RNA transcribed from genomic DNA, and proteins generated by translation of spliced RNA (*i.e.* including proteins both before and after cleavage of normally cleaved regions such as transmembrane signal sequences). As used herein, "marker" may also include a cDNA made by reverse transcription of an RNA generated by transcription of genomic DNA (including spliced RNA). "marker set" is a group of markers. Markers of the present invention include the predictive markers identified in Table 1, Table 2, and Table 3.

[0033] A "Predictive Marker" or "predictive marker" as used herein, includes a marker which has been identified as having differential expression in tumor cells of a patient and is representative of a characteristic of a patient which is responsive in either a positive or negative manner to treatment with a proteasome inhibitor regimen. For example, a predictive marker includes a marker which is upregulated in a non-responsive patient; alternatively a predictive marker includes a marker which is upregulated in a responsive patient. Similarly, a predictive marker is intended to include those markers which are down-regulated in a non-responsive patient as well as those markers which are down-regulated in a responsive patient. Thus, as used herein, predictive marker is intended to include each and every one of these possibilities, and further can include each one individually as a predictive marker; or alternatively can include one or more, or all of the characteristics collectively when reference is made to "predictive markers" or "predictive marker sets."

[0034] As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (*e.g.* encodes a natural protein).

[0035] The term "probe" refers to any molecule which is capable of selectively binding to a specifically intended target molecule, for example a marker of the invention. Probes can be either synthesized by one skilled in the art, or derived from appropriate biological preparations. For purposes of detection of the target molecule, probes may be specifically designed to be labeled, as described herein. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic monomers.

[0036] The "normal" level of expression of a marker is the level of expression of the marker in cells in a similar environment or response situation, in a patient not afflicted with cancer. A normal level of expression of a marker may also refer to the level of expression of a "control sample", (*e.g.,* sample from a healthy subjects not having the marker associated disease). A control sample may be comprised of a control database. Alternatively, a "normal" level of expression of a marker is the level of expression of the marker in non-tumor cells in a similar environment or response situation from the same patient that the tumor is derived from.

[0037] "Over-expression" and "under-expression" of a marker refer to expression of the marker of a patient at a greater or lesser level, respectively, than normal level of expression of the marker (*e.g.* more than one and a half-fold, at least two-fold, at least three-fold, greater or lesser level etc.).

[0038] "Complementary" refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds ("base pairing") with a residue of a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region is capable of base pairing with a residue of the second region. Preferably, the first region comprises a first portion and the second region

comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion. More preferably, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

[0039] "Homologous" as used herein, refers to nucleotide sequence similarity between two regions of the same nucleic acid strand or between regions of two different nucleic acid strands. When a nucleotide residue position in both regions is occupied by the same nucleotide residue, then the regions are homologous at that position. A first region is homologous to a second region if at least one nucleotide residue position of each region is occupied by the same residue. Homology between two regions is expressed in terms of the proportion of nucleotide residue positions of the two regions that are occupied by the same nucleotide residue. By way of example, a region having the nucleotide sequence 5'-ATTGCC-3' and a region having the nucleotide sequence 5'-TATGGC-3' share 50% homology. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residue positions of each of the portions are occupied by the same nucleotide residue. More preferably, all nucleotide residue positions of each of the portions are occupied by the same nucleotide residue.

[0040] A marker is "fixed" to a substrate if it is covalently or non-covalently associated with the substrate such the substrate can be rinsed with a fluid (*e.g.* standard saline citrate, pH 7.4) without a substantial fraction of the marker dissociating from the substrate.

[0041] As used herein, "significant" expression, or a marker "significantly" expressed is intended to refer to differential expression of a predictive marker which is indicative of responsiveness or non-responsiveness. A marker or marker set in a patient is "significantly" expressed at a higher (or lower) level than the normal level of expression of a marker or marker set if the level of expression of the marker or marker set is greater or less, respectively, than the normal level by an amount greater than the standard error of the assay employed to assess expression,. Preferably a significant expression level is at least twice, and more preferably three, four, five or ten times that amount. Alternately, expression of the marker or marker set in the patient can be considered "significantly" higher or lower than the

normal level of expression if the level of expression is at least about two, and preferably at least about three, four, or five times, higher or lower, respectively, than the normal level of expression of the marker or marker set. Still further, a "significant" expression level may refer to level which either meets or is above or below a pre-determined score for a predictive marker set as determined by methods provided herein.

[0042] A cancer or tumor is treated or diagnosed according to the present methods. "Cancer" or "tumor" is intended to include any neoplastic growth in a patient, including an inititial tumor and any metastases. The cancer can be of the liquid or solid tumor type. Liquid tumors include tumors of hematological origin, including, e.g., myelomas (e.g., multiple myeloma), leukemias (e.g., Waldenstrom's syndrome, chronic lymphocytic leukemia, other leukemias), and lymphomas (e.g., B-cell lymphomas, non-Hodgkins lymphoma,). Solid tumors can originate in organs, and include cancers such as lung, breast, prostate, ovary, colon, kidney, and liver. As used herein, cancer cells, including tumor cells, refer to cells that divide at an abnormal (increased) rate. Cancer cells include, but are not limited to, carcinomas, such as squamous cell carcinoma, basal cell carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, adenocarcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, undifferentiated carcinoma, bronchogenic carcinoma, melanoma, renal cell carcinoma, hepatoma-liver cell carcinoma, bile duct carcinoma, cholangiocarcinoma, papillary carcinoma, transitional cell carcinoma, choriocarcinoma, semonoma, embryonal carcinoma, mammary carcinomas, gastrointestinal carcinoma, colonic carcinomas, bladder carcinoma, prostate carcinoma, and squamous cell carcinoma of the neck and head region; sarcomas, such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordosarcoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, synoviosarcoma and mesotheliosarcoma; hematologic cancers, such as myelomas, leukemias (e.g., acute myelogenous leukemia, chronic lymphocytic leukemia, granulocytic leukemia, monocytic leukemia, lymphocytic leukemia), and lymphomas (e.g., follicular lymphoma, mantle cell lymphoma, diffuse large Bcell lymphoma, malignant lymphoma, plasmocytoma, reticulum cell sarcoma, or Hodgkins disease); and tumors of the nervous system including glioma, meningoma, medulloblastoma, schwannoma or epidymoma.

[0043] A cancer is "responsive" to a therapeutic agent if its rate of growth is inhibited as a result of contact with the therapeutic agent, compared to its growth in the absence of contact with the therapeutic agent. Growth of a cancer can be measured in a

variety of ways, for instance, the size of a tumor or the expression of tumor markers appropriate for that tumor type may be measured. For example, the response definitions used to identify markers associated with myeloma and its response to proteasome inhibition therapy, the Southwestern Oncology Group (SWOG) criteria as described in Blade *et al., Br J Haematol.* 1998 Sep;102(5):1115-23 were used (also see e.g., Table C). The quality of being responsive to a proteasome inhibition therapy is a variable one, with different cancers exhibiting different levels of "responsiveness" to a given therapeutic agent, under different conditions. Still further, measures of responsiveness can be assessed using additional criteria beyond growth size of a tumor, including patient quality of life, degree of metastases, etc. In addition, clinical prognostic markers and variables can be assessed (e.g., M protein in myeloma, PSA levels in prostate cancer) in applicable situations.

[0044] A cancer is "non-responsive" to a therapeutic agent if its rate of growth is not inhibited, or inhibited to a very low degree, as a result of contact with the therapeutic agent when compared to its growth in the absence of contact with the therapeutic agent. As stated above, growth of a cancer can be measured in a variety of ways, for instance, the size of a tumor or the expression of tumor markers appropriate for that tumor type may be measured. For example, the response definitions used to identify markers associated with non- response of multiple myeloma to therapeutic agents, the Southwestern Oncology Group (SWOG) criteria as described in Blade *et. al.* were used in the experiments described herein. The quality of being non-responsive to a therapeutic agent is a highly variable one, with different cancers exhibiting different levels of "non-responsiveness" to a given therapeutic agent, under different conditions. Still further, measures of non-responsiveness can be assessed using additional criteria beyond growth size of a tumor, including patient quality of life, degree of metastases, etc. In addition, clinical prognostic markers and variables can be assessed (e.g., M protein in myeloma, PSA levels in prostate cancer) in applicable situations.

[0045] "Treatment" shall mean preventing or inhibiting further tumor growth, as well as causing shrinkage of a tumor. Treatment is also intended to include prevention of metastasis of tumor. A tumor is "inhibited" or "treated" if at least one symptom (as determined by responsiveness/non-responsiveness indicators known in the art and described herein) of the cancer or tumor is alleviated, terminated, slowed, minimized, or prevented. Any amelioration of any symptom, physical or otherwise, of a tumor pursuant to treatment using any proteasome inhibitor, is within the scope of the invention.

[0046] As used herein, the term "agent" is defined broadly as anything that cancer cells, including tumor cells, may be exposed to in a therapeutic protocol. In the context of the present invention, such agents include, but are not limited to, proteasome inhibition agents, as well as chemotherapeutic agents as described in further detail herein.

[0047] "Proteasome inhibitor" shall mean any substance which directly or indirectly inhibits the 20S or 26S proteasome or the activity thereof. Preferably, such inhibition is specific, i.e., the proteasome inhibitor inhibits proteasome activity at a concentration that is lower than the concentration of the inhibitor required to produce another, unrelated biological effect. Preferably, the concentration of the proteasome inhibitor required for proteasome inhibition is at least 2-fold lower, more preferably at least 5-fold lower, even more preferably at least 10-fold lower, and most preferably at least 20-fold lower than the concentration required to produce an unrelated biological effect. Proteasome inhibitors include peptide aldehydes, peptide boronic acids, lactacystin and lactacystin analogues, vinyl sulfones, and alpha.'.beta.'-epoxyketones. Proteasome inhibitors are described in further detail herein.

[0048] A kit is any article of manufacture (*e.g.* a package or container) comprising at least one reagent, *e.g.* a probe, for specifically detecting a marker or marker set of the invention. The article of manufacture may be promoted, distributed, or sold as a unit for performing the methods of the present invention. The reagents included in such a kit comprise probes/primers and/or antibodies for use in detecting responsive and non-predictive marker expression. In addition, the kits of the present invention may preferably contain instructions which describe a suitable detection assay. Such kits can be conveniently used, *e.g.*, in clinical settings, to diagnose and evaluate patients exhibiting symptoms of cancer, in particular patients exhibiting the possible presence of an a cancer capable of treatment with proteasome inhibition therapy, including, e.g., hematological cancers e.g., myelomas (e.g., multiple myeloma), lymphomas (e.g., non-hodgkins lymphoma), leukemias, and solid tumors (e.g., lung, breast, ovarian, etc.).

[0049] The markers of the present invention, whose expression correlates with the response to an agent, are identified in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, and Table 7. By examining the expression of one or more of the identified markers or marker sets in a tumor, it is possible to determine which therapeutic agent or combination of agents will be most likely to reduce the growth rate of the cancer cells. By examining the expression of one or more of the identified markers or marker sets in a cancer, it is also

possible to determine which therapeutic agent or combination of agents will be the least likely to reduce the growth rate of cancer cells. By examining the expression of one or more of the identified markers or marker sets, it is therefore possible to eliminate ineffective or inappropriate therapeutic agents It is also possible to identify new targets for anti-cancer agents by examining the expression of one or more markers or marker sets. Thus, in one embodiment, the tumor cells used in the methods of the present invention are from a bone marrow sample. Importantly, these determinations can be made on a patient by patient basis or on an agent by agent basis. Thus, one can determine whether or not a particular therapeutic treatment is likely to benefit a particular patient or group/class of patients, or whether a particular treatment should be continued.

[0050] Table 1 lists markers identified using statistical analysis applied to genes from 44 myeloma patient samples. The markers in Table 1 are significantly expressed in samples from patients that are either responsive or non-responsive to treatment with the proteasome inhibitor bortezomib. Thus, one would appreciate that the markers identified can function in a predictive model to prospectively identify patients' response to proteasome inhibition therapy, including response to bortezomib or other proteasome inhibition therapies known in the art as well as those described in further detail herein. In particular, the markers in Table 1 are correlated with a positive response to therapy (referred to herein as "responsive markers, (R)"). A patient with a positive response (either complete, partial or minimal; see Table C) to therapy is hereinafter referred to as a "responder". Additionally, the predictive markers in Table 1 are correlated with a negative or poor response to an agent (referred to herein as "non-predictive markers, (NR)"). A patient with a poor response (called a progressive or refractory disease; see Table C) to treatment is hereinafter referred to as a "non-responder". A patient with no response to treatment is hereinafter referred to as "stable" (see Table C).

[0051] Table 2 lists markers identified using statistical analysis applied using a Cox proportional hazard analysis to determine predictors of time until disease progression (TTP) in patients with relapsed and refractory multiple myeloma. These markers are useful as additional predictive markers which are significantly expressed in patients who are likely to progress in disease at a faster rate, and less likely to be responsive to therapy than other patients. These predictive markers will serve as an additional factor in identification of patients likely to be responsive to proteasome inhibition therapy.

[0052] Table 3 lists markers identified using statistical analysis applied to genes from 44 myeloma samples. The predictive markers in Table 2 are significantly expressed in samples from myeloma patients whose disease is refractory to treatment with the proteasome inhibitor bortezomib. These predictive markers will further serve to distinguish refractory patients from those who will be either stable or responsive to treatment.

[0053] The invention also relates to various reagents and kits for diagnosing, staging, prognosing, monitoring and treating a cancer patient, (e.g., a patient with a liquid tumor or a solid tumor as described in further detail herein), with proteasome inhibition therapy.

[0054] According to the invention, the markers are selected such that the positive predictive value of the methods of the invention is at least about 10%, preferably about 25%, more preferably about 50% and most preferably about 90%. Also preferred for use in the methods of the invention are markers that are differentially expressed, as compared to normal cells, by at least two-fold in at least about 20%, more preferably about 50%, and most preferably about 75% of any of the following conditions: responsive patients (e.g., complete response, partial response, minimal response); and non-responsive patients (e.g., no change, relapse from response).

Identification Of Responsive And Non-Predictive markers

[0055] The present invention provides markers that are expressed in a tumor that is responsive to proteasome inhibition therapy and whose expression correlates with responsiveness to that therapeutic agent. The present invention also provides markers that are expressed in a tumor that is non-responsive to proteasome inhibition therapy and whose expression correlates with non-responsiveness to such therapy. Accordingly, one or more of the markers can be used to identify cancers that can be successfully treated by proteasome inhibition therapy. In one embodiment, one or more of the markers of the present invention can be used to identify patients that can be successfully treated using proteasome inhibition therapy. In addition, the markers of the present invention can be used to identify a patient that has become or is at risk of becoming refractory to treatment with proteasome inhibition therapy. The invention also features combinations of markers, referred to herein as "marker sets," that can predict patients that are likely to respond or not to respond to a proteasome inhibition therapy regimen.

[0056] Table 1 identifies markers whose expression correlates with responsiveness to a proteasome inhibitor. It is preferable to determine the expression of at least one, two or

more of the identified predictive markers; or three or more of the identified predictive markers comprising a set of the identified predictive markers.. Thus, it is preferable to assess the expression of a set or panel of predictive markers, *i.e.*, the expression profile of a predictive marker set.

Determining Responsiveness or Non-Responsiveness To An Agent

[0057] The expression level (including protein level) of the identified responsive and non-predictive markers may be used to: 1) determine if a patient can be treated by an agent or combination of agents; 2) determine if a patient is responding to treatment with an agent or combination of agents; 3) select an appropriate agent or combination of agents for treating a patient; 4) monitor the effectiveness of an ongoing treatment; 5) identify new proteasome inhibition therapy treatments (either single agent proteasome inhibitor agents or complementary agents which can be used alternatively or in combination with proteasome inhibition agents); 6) differentiate early versus late recurrence of a cancer; and 7) select an appropriate agent or combination of agents in treating early and late recurrence of a cancer. In particular, the identified responsive and non-predictive markers may be utilized to determine appropriate therapy, to monitor clinical therapy and human trials of a drug being tested for efficacy, and to develop new agents and therapeutic combinations.

[0058] In one embodiment of the invention, a cancer may be predisposed to respond to an agent if one or more of the corresponding predictive markers identified in Table 1, Table 2 and Table 3 are significantly expressed. In another embodiment of the invention, the predisposition of a cancer to be responsive to an agent is determined by the methods of the present invention, wherein significant expression of the individual predictive markers of the marker sets identified in Table 4, Table 5, or Table 6 is evaluated. Likewise, the predisposition of a patient to be responsive to an agent is determined by the methods of the present invention, wherein a marker set generated using to the methods described herein wherein the markers comprising the marker set include predictive markers set forth in Table 1, Table 2, and/or Table 3, and the expression of the marker set is evaluated.

[0059] In another embodiment of the invention, a cancer may be predisposed to non-responsiveness to an agent if one or more of the corresponding non-predictive markers are significantly expressed. In another embodiment of the invention, a cancer may be predisposed to non-responsiveness to an agent if one or more of the corresponding predictive markers identified in Table 1, Table 2 and Table 3 are significantly expressed. In

another embodiment of the invention, the predisposition of a cancer to be non-responsive to an agent is determined by the methods of the present invention, wherein significant expression of the individual predictive markers of the marker sets identified in Table 4, Table 5, or Table 6 is evaluated. Likewise, the predisposition of a patient to be non-responsive to an agent is determined by the methods of the present invention, wherein a marker set is generated using the methods described herein wherein the markers comprising the marker set include predictive markers set forth in Table 1, Table 2, and/or Table 3, and the expression of the marker set is evaluated.

[0060] The present invention provides methods for determining whether a proteasome inhibition therapy *e.g.*, a proteasome inhibitor agent, can be used to reduce the growth rate of a tumor comprising the steps of:

(a) evaluating expression of at least one individual predictive marker in a tumor sample; and

(b) identifying that proteasome inhibition therapy is or is not appropriate to reduce the growth rate of the tumor based on the evaluation.

[0061] In another embodiment, the invention provides a method for determining whether an proteasome inhibition therapeutic regimen (e.g., a proteasome inhibitor agent (e.g., bortezomib) alone or in combination with another chemotherapeutic agent) can be used to reduce the growth rate of a tumor comprising the steps of:

(a) determining the expression profile of a predictive marker or predictive marker set; and

(b) identifying that a proteasome inhibition therapeutic agent is or is not appropriate to reduce the growth rate of the myeloma cells based on the expression profile.

[0062] In one aspect, the predictive marker or markers evaluated are selected from those set forth in Table 1. In yet another aspect the predictive marker or markers evaluated are selected from those set forth in Table 2. In still another aspect the predictive marker or markers evaluated are selected from those set forth in Table 3. Still a further aspect contemplates markers set forth in either Table 1 alone or in combination with markers set for the in Table 2 and/or Table 3, or alternatively, those markers set forth in Table 2 alone or in combination with Table 1 and/or Table 3.

[0063] In another embodiment, the invention provides a method for determining whether a proteasome inhibitor therapy can be used to reduce the growth of a tumor, comprising the steps of:

(a) obtaining a sample of tumor cells;

(b) evaluating the expression of one or more individual markers of a marker set, both in tumor cells exposed to the agent and in tumor cells that have not been exposed to the proteasome inhibition therapy; and

(c) identifying that an agent is or is not appropriate to treat the tumor based on the evaluation.

[0064] In such methods, a proteasome inhibition therapy regimen is determined appropriate to treat the tumor when the expression profile of the marker set demonstrates increased responsiveness or decreased non-responsiveness according to the expression profile of the predictive markers in the presence of the agent

[0065] In a preferred embodiment, the predictive markers are selected from those set forth in Table 1, Table 2 or Table 3.

[0066] In another embodiment, the invention provides a method for determining whether treatment with an anti-cancer agent should be continued in an multiple myeloma patient, comprising the steps of:

(a) obtaining two or more samples of tumor cells from a patient at different times during the course of an proteasome inhibition therapy treatment;

(b) evaluating the expression of the individual markers of a marker set, in the two or more samples; and

(c) continuing or discontinuing the treatment based on the evaluation.

[0067] In a preferred embodiment, the marker set is selected from those set forth in Table 1 or Table 2 or Table 3. According to the methods, proteasome inhibition therapy would be continued where the expression profile indicates continued responsiveness, or decreased non-responsiveness using the evaluation methods described herein.

[0068] In another embodiment, the invention provides a method for determining whether treatment with a proteasome inhibition therapy regimen should be continued in an myeloma patient, comprising the steps of:

(a) obtaining two or more samples of myeloma cells from a patient at different times during the course of anti-cancer agent treatment;

(b) determining the expression profile a predictive marker set, in the two or more samples; and

(c) continuing the treatment when the expression profile of the predictive marker set does not demonstrate decreased responsiveness and/or does not demonstrate increased non-responsive during the course of treatment.

[0069] Alternatively, in step (c), the treatment is discontinued when the expression profile of the marker set demonstrates decreased responsiveness and/or increased non-responsiveness during the course of treatment. In a preferred embodiment, the marker set is selected from those set forth in Table 1, Table 2 or Table 3.

[0070] The present invention further provides methods for determining whether an agent, *e.g.*, a chemotherapeutic agent, can be used to reduce the growth rate of multiple myeloma comprising the steps of:

(a) obtaining a sample of cancer cells;

[0071] In another embodiment, the invention provides a method for determining whether treatment with an anti-cancer agent should be continued in an multiple myeloma patient, comprising the steps of:

obtaining two or more samples of myeloma cells from a patient at different times during the course of anti-cancer agent treatment;

determining the level of expression in the myeloma cells of one or more genes which correspond to markers identified in any of Table 1, Table 2 or Table 3 in the two or more samples; and

[0072] continuing the treatment is continued when the expression profile of the predictive markers identified in any one of Table 1, Table 2, and Table 3 is indicative of a responsive patient during the course of treatment.

[0073] Alternatively, in step (c), the treatment is discontinued when the expression profile of the predictive markers identified in any one of Table 1, Table 2 and Table 3 is indicative of a non-responsive patient during the course of treatment

[0074] In another embodiment, the invention provides a method for determining whether treatment with bortezomib should be continued in an multiple myeloma patient, comprising the steps of:

obtaining two or more samples of myeloma cells from a patient at different times during the course of treatment with bortezomib;

determining the expression profile in the myeloma cells of one or more genes which correspond to markers identified in Table 1 Table 2 or Table 3 in the two or more samples; and

continuing the treatment when the expression profile of the predictive markers identified in Table 1 Table 2 or Table 3 is indicative of a responsive patient. Alternatively, the treatment is discontinued when the expression profile of the predictive markers identified in Table 1 Table 2 and/or Table 3 is indicative of a non-responsive patient during the course of treatment

[0075] The markers and marker sets of the present invention are predictive of proteasome inhibition therapy regimens, generally. Proteasome inhibition therapy, generally comprises at least an agent which inhibition proteasome activity in a cell, and can comprise additional therapeutic agents. In one embodiment of the invention, the agent used in methods of the invention is a proteasome inhibitor. In certain aspects, the proteasome inhibitor is bortezomib, or other related proteasome inhibitor agents as described in further detail herein. Still other aspects, the proteasome inhibition therapy comprises a proteasome inhibitor agent in conjunction with a chemotherapeutic agent. Chemotherapeutic agents are known in the art and described in further detail herein.

[0076] In another embodiment of the invention, the expression of predictive marker or markers identified in Table 1, Table 2, and Table 3 is detected by measuring mRNA which corresponds to the predictive marker. In yet another embodiment of the invention, the expression of markers which correspond to markers or marker sets identified in Table 1 Table 2 and Table 3, is detected by measuring protein which corresponds to the marker.

[0077] In another embodiment, the invention provides a method of treating a patient with cancer by administering to the patient a compound which has been identified as being effective against a cancer by the methods of the invention described herein.

[0078] The source of the cancer cells used in the present method will be based on how the method of the present invention is being used. For example, if the method is being used to determine whether a patient's cancer can be treated with an agent, or a combination of agents, then the preferred source of cancer cells will be cancer cells obtained from a tumor from the patient, *e.g.*, a tumor biopsy (including a solid or a liquid tumor), a blood sample. Alternatively, a cancer cell line similar to the type of cancer being treated can be assayed. For example if multiple myeloma is being treated, then a myeloma cell line can be used. If the method is being used to predict or monitor the effectiveness of a therapeutic protocol, then a tissue or blood sample from the patient being treated is the preferred source. If the method is being used to identify new therapeutic agents or combinations, any cancer cells, *e.g.*, cells of a cancer cell line, can be used.

[0079] A skilled artisan can readily select and obtain the appropriate cancer cells that are used in the present method. For cancer cell lines, sources such as The National Cancer Institute, for the NCI-60 cells, are preferred. For cancer cells obtained from a patient, standard biopsy methods, such as a needle biopsy, can be employed.

[0080] Myeloma samples were used to identify the markers of the present invention. Further, the expression level of markers can be evaluated in other tissue types including disorders of related hematological cell types, including, e.g., Waldenstroms macrogobulinemia, Myelodysplastic syndrome and other hematological cancers including lymphomas, leukemias, as well as tumors of various solid tissues. It will thus be appreciated that cells from other hematologic malignancies including, e.g., B-cell Lymphomas, Non-Hodgkins Lymphoma, Waldenstrom's syndrome, or other leukemias will be useful in the methods of the present invention. Still further, the predictive markers predicting disease aggressiveness as well as responsiveness and non-responsiveness to proteasome inhibition therapeutic agents in solid tumors (e.g., lung, breast, prostate, ovary, colon, kidney, and liver), can also be useful in the methods of the present invention.

[0081] In the methods of the present invention, the level of expression of one or more predictive markers selected from the group consisting of the markers identified in Table 1 Table 2 and Table 3, is determined. As used herein, the level or amount of expression refers to the absolute level of expression of an mRNA encoded by the marker or the absolute level of expression of the protein encoded by the marker (*i.e.*, whether or not expression is or is not occurring in the cancer cells).

[0082] Generally, it is preferable to determine the expression of two or more of the identified responsive or non-predictive markers, or three or more of the identified responsive or non-predictive markers, or still further a larger a set of the identified responsive and/or non-predictive markers, selected from the predictive markers identified in Table 1, Table 2 and Table 3. For example, Table 4, Table 5 and Table 6 set forth marker sets identified using the methods described herein and can be used in the methods of the present invention. Still further, additional and/or alternative marker sets comprising the predictive markers identified herein can be generated using the methods and predictive markers provided. Thus, it is possible to assess the expression of a panel of responsive and non-predictive markers using the methods and compositions provided herein.

[0083] As an alternative to making determinations based on the absolute expression level of selected markers, determinations may be based on normalized expression levels.

Expression levels are normalized by correcting the absolute expression level of a responsive or non-predictive marker by comparing its expression to the expression of a control marker that is not a responsive or non-predictive marker, *e.g.*, a housekeeping gene that is constitutively expressed. Suitable markers for normalization include housekeeping genes, such as the actin gene. Constitutively expressed genes are known in the art and can be identified and selected according to the relevant tissue and/or situation of the patient and the analysis methods. Such normalization allows one to compare the expression level in one sample, *e.g.*, a tumor sample, to another sample, *e.g.*, a non-tumor sample, or between samples from different sources.

[0084] Further, the expression level can be provided as a relative expression level. To determine a relative expression level of a marker or marker set, the level of expression of the predictive marker or marker set is determined for 10 or more individual samples, preferably 50 or more individual samples in order to establish a baseline, prior to the determination of the expression level for the sample in question. To establish a baseline measurement, mean expression level of each of the predictive markers or marker sets assayed in the larger number of samples is determined and this is used as a baseline expression level for the predictive markers or marker sets in question. The expression level of the marker or marker set determined for the test sample (absolute level of expression) is then divided by the mean expression value obtained for that marker or marker set. This provides a relative expression level and aids in identifying extreme cases of responsive or non-responsive-ness.

[0085] Preferably, the samples used will be from similar tumors or from non-cancerous cells of the same tissue origin as the tumor in question. The choice of the cell source is dependent on the use of the relative expression level data. For example, using tumors of similar types for obtaining a mean expression score allows for the identification of extreme cases of responsive or non-responsive-ness. Using expression found in normal tissues as a mean expression score aids in validating whether the responsive/non-predictive marker or marker set assayed is tumor specific (versus normal cells). Such a later use is particularly important in identifying whether a responsive or non-predictive marker or marker set can serve as a target marker or marker set. In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data.

[0086] Still further, as outlined above, there are various methods available to examine the expression of the markers, including gene array/chip technology, RT-PCR, in-situ hybridization, immunohistochemistry, immunoblotting, FISH (flouresence in-situ hybridization), FACS analyses, northern blot, southern blot or cytogenetic analyses. A skilled artisan can select from these or other appropriate and available methods based on the nature of the marker(s), tissue sample and disease in question. Different methods or combinations of methods could be appropriate in different cases or, for instance in different solid or hematological tumor types.

Detection Assays

[0087] An exemplary method for detecting the presence or absence of a polypeptide or nucleic acid corresponding to a marker of the invention in a biological sample involves obtaining a biological sample (*e.g.* a tumor sample) from a test subject and contacting the biological sample with a compound or an agent capable of detecting the polypeptide or nucleic acid (*e.g.*, mRNA, genomic DNA, or cDNA). The detection methods of the invention can thus be used to detect mRNA, protein, cDNA, or genomic DNA, for example, in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of mRNA include Northern hybridizations . *in situ* hybridizations, and TaqMan assays (Applied Biosystems) under GLP approved laboratory conditions. *In vitro* techniques for detection of a polypeptide corresponding to a marker of the invention include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of a polypeptide corresponding to a marker of the invention include introducing into a subject a labeled antibody directed against the polypeptide. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

[0088] A general principle of such diagnostic and prognostic assays involves preparing a sample or reaction mixture that may contain a marker, and a probe, under appropriate conditions and for a time sufficient to allow the marker and probe to interact and bind, thus forming a complex that can be removed and/or detected in the reaction mixture. These assays can be conducted in a variety of ways.

[0089] For example, one method to conduct such an assay would involve anchoring the marker or probe onto a solid phase support, also referred to as a substrate, and detecting target marker/probe complexes anchored on the solid phase at the end of the reaction. In one embodiment of such a method, a sample from a subject, which is to be assayed for presence and/or concentration of marker, can be anchored onto a carrier or solid phase support. In another embodiment, the reverse situation is possible, in which the probe can be anchored to a solid phase and a sample from a subject can be allowed to react as an unanchored component of the assay. One example of such an embodiment includes use of an array or chip which contains a predictive marker or marker set anchored for expression analysis of the sample.

[0090] There are many established methods for anchoring assay components to a solid phase. These include, without limitation, marker or probe molecules which are immobilized through conjugation of biotin and streptavidin. Such biotinylated assay components can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the surfaces with immobilized assay components can be prepared in advance and stored.

[0091] Other suitable carriers or solid phase supports for such assays include any material capable of binding the class of molecule to which the marker or probe belongs. Well-known supports or carriers include, but are not limited to, glass, polystyrene, nylon, polypropylene, nylon, polyethylene, dextran, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

[0092] In order to conduct assays with the above mentioned approaches, the non-immobilized component is added to the solid phase upon which the second component is anchored. After the reaction is complete, uncomplexed components may be removed (*e.g.*, by washing) under conditions such that any complexes formed will remain immobilized upon the solid phase. The detection of marker/probe complexes anchored to the solid phase can be accomplished in a number of methods outlined herein.

[0093] In a preferred embodiment, the probe, when it is the unanchored assay component, can be labeled for the purpose of detection and readout of the assay, either directly or indirectly, with detectable labels discussed herein and which are well-known to one skilled in the art.

[0094] It is also possible to directly detect marker/probe complex formation without further manipulation or labeling of either component (marker or probe), for example by utilizing the technique of fluorescence energy transfer (see, for example, Lakowicz *et al.*, U.S. Patent No. 5,631,169; Stavrianopoulos, *et al.*, U.S. Patent No. 4,868,103). A fluorophore label on the first, 'donor' molecule is selected such that, upon excitation with incident light of appropriate wavelength, its emitted fluorescent energy will be absorbed by a fluorescent label on a second 'acceptor' molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter).

[0095] In another embodiment, determination of the ability of a probe to recognize a marker can be accomplished without labeling either assay component (probe or marker) by utilizing a technology such as real-time Biomolecular Interaction Analysis (BIA) (see, *e.g.*, Sjolander, S. and Urbaniczky, C., 1991, *Anal. Chem.* 63:2338-2345 and Szabo *et al.*, 1995, *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" or "surface plasmon resonance" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index of light near the surface (the optical phenomenon of surface plasmon resonance (SPR)), resulting in a detectable signal which can be used as an indication of real-time reactions between biological molecules.

[0096] Alternatively, in another embodiment, analogous diagnostic and prognostic assays can be conducted with marker and probe as solutes in a liquid phase. In such an assay, the complexed marker and probe are separated from uncomplexed components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, marker/probe complexes may be separated from uncomplexed assay components through a

series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., 1993, *Trends Biochem Sci.* 18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the marker/probe complex as compared to the uncomplexed components may be exploited to differentiate the complex from uncomplexed components, for example through the utilization of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, *e.g.*, Heegaard, N.H., 1998, *J. Mol. Recognit.* Winter 11(1-6):141-8; Hage, D.S., and Tweed, S.A. *J Chromatogr B Biomed Sci Appl* 1997 Oct 10;699(1-2):499-525). Gel electrophoresis may also be employed to separate complexed assay components from unbound components (see, *e.g.*, Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, 1987-1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, non-denaturing gel matrix materials and conditions in the absence of reducing agent are typically preferred. Appropriate conditions to the particular assay and components thereof will be well known to one skilled in the art.

[0097] In a particular embodiment, the level of mRNA corresponding to the marker can be determined both by *in situ* and by *in vitro* formats in a biological sample using methods known in the art. The term "biological sample" is intended to include tissues, cells, biological fluids and isolates thereof, isolated from a subject, as well as tissues, cells and fluids present within a subject. Many expression detection methods use isolated RNA. For *in vitro* methods, any RNA isolation technique that does not select against the isolation of mRNA can be utilized for the purification of RNA from tumor cells (see, *e.g.*, Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York 1987-1999). Additionally, large numbers of tissue samples can readily be processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski (1989, U.S. Patent No. 4,843,155).

[0098] The isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction

and TaqMan analyses and probe arrays. One preferred diagnostic method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to a mRNA or genomic DNA encoding a marker of the present invention. Other suitable probes for use in the diagnostic assays of the invention are described herein. Hybridization of an mRNA with the probe indicates that the marker in question is being expressed.

[0099] In one format, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative format, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in detecting the level of mRNA encoded by the markers of the present invention.

[00100] An alternative method for determining the level of mRNA corresponding to a marker of the present invention in a sample involves the process of nucleic acid amplification, *e.g.*, by rtPCR (the experimental embodiment set forth in Mullis, 1987, U.S. Patent No. 4,683,202), ligase chain reaction (Barany, 1991, *Proc. Natl. Acad. Sci. USA,* 88:189-193), self sustained sequence replication (Guatelli *et al.*, 1990, *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.*, 1988, *Bio/Technology* 6:1197), rolling circle replication (Lizardi *et al.*, U.S. Patent No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. As used herein, amplification primers are defined as being a pair of nucleic acid molecules that can anneal to 5' or 3' regions of a gene (plus and minus strands, respectively, or vice-versa) and contain a short region in between. In general, amplification primers are from about 10 to 30 nucleotides in length and flank a region from about 50 to 200 nucleotides in length. Under appropriate conditions and with appropriate reagents, such

primers permit the amplification of a nucleic acid molecule comprising the nucleotide sequence flanked by the primers.

[00101] For *in situ* methods, mRNA does not need to be isolated from the cancer cells prior to detection. In such methods, a cell or tissue sample is prepared/processed using known histological methods. The sample is then immobilized on a support, typically a glass slide, and then contacted with a probe that can hybridize to mRNA that encodes the marker.

[00102] As an alternative to making determinations based on the absolute expression level of the marker, determinations may be based on the normalized expression level of the marker. Expression levels are normalized by correcting the absolute expression level of a marker by comparing its expression to the expression of a control gene that is not a marker, *e.g.*, a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene, or epithelial cell-specific genes. This normalization allows the comparison of the expression level in one sample, *e.g.*, a patient sample, to another sample, *e.g.*, a non- cancer sample, or between samples from different sources.

[00103] Alternatively, the expression level can be provided as a relative expression level. To determine a relative expression level of a marker, the level of expression of the marker is determined for 10 or more samples of normal versus cancer cell isolates, preferably 50 or more samples, prior to the determination of the expression level for the sample in question. The mean expression level of each of the markers and marker sets assayed in the larger number of samples is determined and this is used as a baseline expression level for the marker. The expression level of the marker determined for the test sample (absolute level of expression) is then divided by the mean expression value obtained for that marker. This provides a relative expression level.

[00104] In another embodiment of the present invention, a polypeptide corresponding to a marker is detected. A preferred agent for detecting a polypeptide of the invention is an antibody capable of binding to a polypeptide corresponding to a marker of the invention, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or $F(ab')_2$) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include

detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

[00105] A variety of formats can be employed to determine whether a sample contains a protein that binds to a given antibody. Examples of such formats include, but are not limited to, enzyme immunoassay (EIA), radioimmunoassay (RIA), Western blot analysis and enzyme linked immunoabsorbant assay (ELISA). A skilled artisan can readily adapt known protein/antibody detection methods for use in determining whether cancer cells express a marker of the present invention.

[00106] In one format, antibodies, or antibody fragments, can be used in methods such as Western blots or immunofluorescence techniques to detect the expressed proteins. In such uses, it is generally preferable to immobilize either the antibody or proteins on a solid support. Suitable solid phase supports or carriers include any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

[00107] One skilled in the art will know many other suitable carriers for binding antibody or antigen, and will be able to adapt such support for use with the present invention. For example, protein isolated from tumor cells can be run on a polyacrylamide gel electrophoresis and immobilized onto a solid phase support such as nitrocellulose. The support can then be washed with suitable buffers followed by treatment with the detectably labeled antibody. The solid phase support can then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on the solid support can then be detected by conventional means.

[00108] The invention also encompasses kits for detecting the presence of a polypeptide or nucleic acid corresponding to a marker of the invention in a biological sample (*e.g.* an ovary-associated body fluid such as a urine sample). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing cancer. For example, the kit can comprise a labeled compound or agent capable of detecting a polypeptide or an mRNA encoding a polypeptide corresponding to a marker of the invention in a biological sample and means for determining the amount of the polypeptide or mRNA in the sample (*e.g.*, an antibody which binds the polypeptide or an oligonucleotide probe

which binds to DNA or mRNA encoding the polypeptide). Kits can also include instructions for interpreting the results obtained using the kit.

[00109] For antibody-based kits, the kit can comprise, for example: (1) a first antibody (*e.g.*, attached to a solid support) which binds to a polypeptide corresponding to a marker of the invention; and, optionally, (2) a second, different antibody which binds to either the polypeptide or the first antibody and is conjugated to a detectable label.

[00110] For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, *e.g.*, a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a polypeptide corresponding to a marker of the invention; (2) a pair of primers useful for amplifying a nucleic acid molecule corresponding to a marker of the invention; or (3) a marker set comprising oligonucleotides which hybridize to at least two nucleic acid sequences encoding polypeptide predictive markers of the invention. The kit can also comprise, *e.g.*, a buffering agent, a preservative, or a protein stabilizing agent. The kit can further comprise components necessary for detecting the detectable label (*e.g.*, an enzyme or a substrate). For marker sets, the kit can comprise a marker set array or chip for use in detecting the predictive markers. The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit.

Monitoring the Effectiveness of an Anti-Cancer Agent

[00111] As discussed above, the identified responsive and non-predictive markers can be used as pharmacodynamic markers to assess whether the tumor has become refractory to an ongoing treatment (*e.g.*, a proteasome inhibition therapy). When the cancer is not responding to a treatment the expression profile of the tumor cells will change: the level or relative expression of one or more of the predictive markers (e.g., those predictive markers identified in Table 1, Table 2, Table 3) such that the expression profile represents a non-responsive patient.

[00112] In one such use, the invention provides methods for determining whether a proteasome inhibition treatment should be continued in a cancer patient, comprising the steps of:

determining the expression of at least one predictive marker of a marker set, wherein the markers are selected from those set forth in any of Table 1, Table 2 or Table 3, in a tumor sample of a patient exposed to a proteasome inhibition therapy; and
continuing treatment when the expression profile of the marker or marker set demonstrates responsiveness to the agent being used.

[00113] In another such use, the invention provides methods for determining whether a proteasome inhibition therapy should be discontinued in a cancer patient, comprising the steps of:

determining the expression of at least one predictive marker of a marker set, wherein the markers are selected from those set forth in any of Table 1, Table 2 or Table 3 in a tumor sample of a patient expose to a proteasome inhibition therapy; and
discontinuing or altering treatment when the expression profile of the markers identified in any one of Table 1 Table 2 or Table 3 demonstrates non-responsiveness to the agent being used.

[00114] As used herein, a patient refers to any subject undergoing proteasome inhibition therapy for cancer treatment. In one embodiment, the subject will be a human patient undergoing proteasome inhibition using a sole proteasome inhibition agent (e.g., bortezomib or other related agent). In another embodiment, the subject is a human patient undergoing proteasome inhibition using a proteasome inhibition agent in conjunction with another agent (e.g., a chemotherapy treatment). This embodiment of the present invention can also include comparing two or more samples obtained from a patient undergoing anti-cancer treatment including proteasome inhibition therapy. In general, it is conceivable to obtain a first sample from the patient prior to beginning therapy and one or more samples during treatment. In such a use, a baseline of expression prior to therapy is determined, then changes in the baseline state of expression is monitored during the course of therapy. Alternatively, two or more successive samples obtained during treatment can be used without the need of a pre-treatment baseline sample. In such a use, the first sample obtained from the subject is used as a baseline for determining whether the expression of a particular marker or marker set is increasing or decreasing.

[00115] In general, when monitoring the effectiveness of a therapeutic treatment, two or more samples from a patient are examined. In another aspect, three or more successively obtained samples are used, including at least one pretreatment sample.

Electronic Apparatus Readable Arrays

[00116] Electronic apparatus readable arrays comprising at least one predictive marker orof the present invention is also provided. As used herein, "electronic apparatus readable media" refers to any suitable medium for storing, holding or containing data or information that can be read and accessed directly by an electronic apparatus. As used herein, the term "electronic apparatus" is intended to include any suitable computing or processing apparatus or other device configured or adapted for storing data or information. Examples of electronic apparatus suitable for use with the present invention include stand-alone computing apparatus; networks, including a local area network (LAN), a wide area network (WAN) Internet, Intranet, and Extranet; electronic appliances such as a personal digital assistants (PDAs), cellular phone, pager and the like; and local and distributed processing systems. As used herein, "recorded" refers to a process for storing or encoding information on the electronic apparatus readable medium. Those skilled in the art can readily adopt any of the presently known methods for recording information on known media to generate manufactures comprising the markers of the present invention.

[00117] The array can be used to assay expression of one or more predictive markers or predictive marker sets in the array. In one embodiment, the array can be used to assay predictive marker or marker set expression in a tissue to ascertain tissue specificity of markers in the array. In this manner, up to about 44,000 markers can be simultaneously assayed for expression. This allows a profile to be developed showing a battery of markers specifically expressed in one or more tissues.

[00118] The array is also useful for ascertaining differential expression patterns of one or more markers in normal and abnormal (e.g., tumor) cells. This provides a battery of predictive markers that could serve as a tool for ease of identification of responsive and non-responsive patients.

[00119] In addition to such qualitative determination, the invention allows the quantitation of marker expression. Thus, predictive markers can be grouped on the basis of marker sets or responsive and non-responsive indications by the level of expression in the sample. This is useful, for example, in ascertaining the responsive or non-responsive indication of the sample by virtue of scoring the expression levels according to the methods provided herein.

[00120] In another embodiment, the array can be used to monitor the time course of expression of one or more predictive markers in the array.

[00121] The array is also useful for ascertaining the effect of the expression of a marker on the expression of other predictive markers in the same cell or in different cells. This provides, for example, a selection of alternate molecular targets for therapeutic intervention if the proteasome inhibition regimen is non-responsive.

Therapeutic Agents

[00122] The markers of the present invention are shown to be predictive of patients who are responsive or non-responsive (sensitive or resistant) to proteasome inhibition therapy. Proteasome inhibition therapy can comprise treatment of a cancer patient with a proteasome inhibitor agent, alone or in combination with additional agents, such as chemotherapeutic agents.

[00123] The examples described herein entail use of the proteasome inhibitor *N*-pyrazinecarbonyl-L-phenylalanine-L-leucineboronic acid, bortezomib ((VELCADE™); formerly known as MLN341 or PS-341). The language "proteasome inhibitor" is intended to include bortezomib, compounds which are structurally similar to bortezomib and/or analogs of bortezomib. The language "proteasome inhibitor" can also include "mimics". "Mimics" is intended to include compounds which may not be structurally similar to bortezomib but mimic the therapeutic activity of bortezomib or structurally similar compounds *in vivo*. Proteasome inhibitor compounds of this invention are those compounds which are useful for inhibiting tumor growth, (e.g., multiple myeloma tumor growth, other hematological or solid tumors as described in further detail herein) in patients. Proteasome inhibitor also is intended to include pharmaceutically acceptable salts of the compounds.

[00124] Proteasome inhibitors for use in the practice of the invention include additional peptide boronic acids such as those disclosed in Adams *et al.*, U.S. Patent No. 5,780,454 (1998), U.S. Patent No. 6,066,730 (2000), U.S. Patent No. 6,083,903 (2000), U.S. Patent No. 6,548,668 (2003), and Siman et al. WO 91/13904, each of which is hereby incorporated by reference in its entirety, including all compounds and formulae disclosed therein. Preferably, a boronic acid compound for use in the present invention is selected from the group consisting of: N-(4-morpholine)carbonyl-.beta.-(1-naphthyl)-L-alanine-L-leucine boronic acid; N-(8-quinoline)sulfonyl-.beta.-(1-naphthyl)-L-alanine-L-alanine-L-leucine boronic acid; N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid, and N-(4-morpholine)carbonyl-[O-(2-pyridylmethyl)]-L-tyrosine-L-leucine boronic acid.

[00125] Additionally, proteasome inhibitors include peptide aldehyde proteasome inhibitors such as those disclosed in Stein et al. U.S. Patent No. 5,693,617 (1997), and International patent publications WO 95/24914 published Sep. 21, 1995 and Siman et al. WO 91/13904 published Sep. 19, 1991; Iqbal et al. J. Med. Chem. 38:2276-2277 (1995), as well as Bouget et al. Bioorg Med Chem 17:4881-4889 (2003) each of which is hereby incorporated by reference in its entirety, including all compounds and formulae disclosed therein.

[00126] Further, proteasome inhibitors include lactacystin and lactacycstin analogs which have been disclosed in Fentany et al, U.S. Patent No. 5,756,764 (1998), and U.S. Patent No. 6,147,223(2000), Schreiber et al U.S. Patent No. 6,645,999 (2003), and Fenteany et al. Proc. Natl. Acad. Sci. USA (1994) 91:3358, each of which is hereby incorporated by reference in its entirety, including all compounds and formulae disclosed therein.

[00127] Additionally, synthetic peptide vinyl sulfone proteasome inhibitors and epoxyketone proteasome inhibitors have been disclosed and are useful in the methods of the invention. See, e.g., Bogyo et al., Proc. Natl. Acad. Sci. 94:6629 (1997); Spaltensteinet al. Tetrahedron Lett. 37:1343 (1996); Meng L, Proc. Natl. Acad Sci 96: 10403 (1999); and Meng LH, Cancer Res 59: 2798 (1999), each of which is hereby incorporated by reference in its entirety.

[00128] Still further, natural compounds have been recently shown to have proteasome inhibition activity can be used in the present methods. For example, TMC-95A, a cyclic peptide, or Gliotoxin, both fungal metabolites or polyphenols compounds found in green tea have been identified as proteasome inhibitors. See, e.g., Koguchi Y, Antibiot (Tokyo) 53:105. (2000); Kroll M, Chem Biol 6:689 (1999); and Nam S, J. Biol Chem 276: 13322(2001), each of which is hereby incorporated by reference in its entirety.

[00129] Further to the above, the language, proteasome inhibition therapy can also include additional agents in addition to proteasome inhibition agents, including chemotherapeutic agents. A "chemotherapeutic agent" is intended to include chemical reagents which inhibit the growth of proliferating cells or tissues wherein the growth of such cells or tissues is undesirable. Chemotherapeutic agents such as anti-metabolic agents, *e.g.*, Ara AC, 5-FU and methotrexate, antimitotic agents, *e.g.*, taxane, vinblastine and vincristine, alkylating agents, *e.g.*, melphanlan, BCNU and nitrogen mustard, Topoisomerase II inhibitors, *e.g.*, VW-26, topotecan and Bleomycin, strand-breaking agents, *e.g.*, doxorubicin and DHAD, cross-linking agents, *e.g.*, cisplatin and CBDCA, radiation and

ultraviolet light. In a preferred embodiment, the agent is a proteasome inhibitor (*e.g.*, bortezomib or other related compounds).are well known in the art (see *e.g.*, Gilman A.G., et al., The Pharmacological Basis of Therapeutics, 8th Ed., Sec 12:1202-1263 (1990)), and are typically used to treat neoplastic diseases. The chemotherapeutic agents generally employed in chemotherapy treatments are listed below in Table A.

TABLE A

CLASS	TYPE OF AGENT	NONPROPRIETARY NAMES (OTHER NAMES)
Alkylating	Nitrogen Mustards	Mechlorethamine (HN_2) Cyclophosphamide Ifosfamide Melphalan (L-sarcolysin) Chlorambucil
	Ethylenimines And Methylmelamines	Hexamethylmelamine Thiotepa
	Alkyl Sulfonates	Busulfan
Alkylating	Nitrosoureas	Carmustine (BCNU) Lomustine (CCNU) Semustine (methyl-CCNU) Streptozocin (streptozotocin)
	Triazenes	Decarbazine (DTIC; dimethyltriazenoimi-dazolecarboxamide)
Alkylating	Alkylator	cis-diamminedichloroplatinum II (CDDP)
Antimetabolites	Folic Acid Analogs	Methotrexate (amethopterin)
	Pyrimidine Analogs	Fluorouracil ('5-fluorouracil; 5-FU) Floxuridine (fluorode-oxyuridine; FUdR) Cytarabine (cytosine arabinoside)
	Purine Analogs and Related Inhibitors	Mercaptopuine (6-mercaptopurine; 6-MP) Thioguanine (6-thioguanine; TG) Pentostatin (2' - deoxycoformycin)
Natural Products	Vinca Alkaloids	Vinblastin (VLB) Vincristine
	Topoisomerase Inhibitors	Etoposide Teniposide Camptothecin Topotecan 9-amino-campotothecin CPT-11
	Antibiotics	Dactinomycin (actinomycin D) Adriamycin Daunorubicin (daunomycin; rubindomycin) Doxorubicin Bleomycin Plicamycin (mithramycin) Mitomycin (mitomycin C) TAXOL Taxotere
	Enzymes	L-Asparaginase

TABLE A CONTINUED

CLASS	TYPE OF AGENT	NONPROPRIETARY NAMES (OTHER NAMES)
Natural Products	Biological Response Modifiers	Interfon alfa Interleukin 2
Miscellaneous Agents	Platinum Coordination Complexes	cis-diamminedichloroplatinum II (CDDP) Carboplatin
	Anthracendione	Mitoxantrone
	Substituted Urea	Hydroxyurea
	Methyl Hydraxzine Derivative	Procarbazine (N-methylhydrazine,(MIH)
	Adrenocortical Suppressant	Mitotane (o,p'-DDD) Aminoglutethimide
Hormones and Antagonists	Adrenocorticosteroids	Prednisone
	Progestins	Hydroxyprogesterone caproate Medroxyprogesterone acetate Megestrol acetate
	Estrogens	Diethylstilbestrol Ethinyl estradiol
	Antiestrogen	Tamoxifen
	Androgens	Testosterone propionate Fluoxymesterone
	Antiandrogen	Flutamide
	Gonadotropin-releasing Hormone analog	Leuprolide

[00130] The agents tested in the present methods can be a single agent or a combination of agents. For example, the present methods can be used to determine whether a single chemotherapeutic agent, such as methotrexate, can be used to treat a cancer or whether a combination of two or more agents can be used in combination with a proteasome inhibitor. Preferred combinations will include agents that have different mechanisms of action, *e.g.*, the use of an anti-mitotic agent in combination with an alkylating agent and a proteasome inhibitor.

[00131] The agents disclosed herein may be administered by any route, including intradermally, subcutaneously, orally, intraarterially or intravenously. Preferably, administration will be by the intravenous route. Preferably parenteral administration may be provided in a bolus or by infusion.

[00132] The concentration of a disclosed compound in a pharmaceutically acceptable mixture will vary depending on several factors, including the dosage of the compound to be administered, the pharmacokinetic characteristics of the compound(s) employed, and the route of administration. Effective amounts of agents for treating ischemia or reperfusion injury would broadly range between about 10 μg and about 50 mg per Kg of body weight of a recipient mammal. The agent may be administered in a single dose or in repeat doses.

Treatments may be administered daily or more frequently depending upon a number of factors, including the overall health of a patient, and the formulation and route of administration of the selected compound(s).

Isolated Nucleic Acid Molecules, Vectors and Host Cells

[00133] One aspect of the invention pertains to isolated nucleic acid molecules that correspond to a predictive marker of the invention, including nucleic acids which encode a polypeptide corresponding to a predictive marker of the invention or a portion of such a polypeptide. Isolated nucleic acids of the invention also include nucleic acid molecules sufficient for use as hybridization probes to identify nucleic acid molecules that correspond to a predictive marker of the invention, including nucleic acids which encode a polypeptide corresponding to a predictive marker of the invention, and fragments of such nucleic acid molecules, *e.g.*, those suitable for use as PCR primers for the amplification or mutation of nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

[00134] A nucleic acid molecule of the present invention, *e.g.*, a nucleic acid encoding a protein corresponding to a marker listed in any one of Table 1, Table 2, and/or Table 3, can be isolated and manipulated (e.g., amplified, cloned, synthesized, etc.) using standard molecular biology techniques and the sequence information in the database records described herein. (*e.g.*, described in Sambrook *et al.*, ed., *Molecular Cloning: A Laboratory Manual, 2nd ed.,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

[00135] Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence, wherein the full length nucleic acid sequence comprises a predictive marker of the invention or which encodes a polypeptide corresponding to a marker of the invention. Such nucleic acids can be used, for example, as a probe or primer. The probe/primer typically is used as one or more substantially purified oligonucleotides. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 7, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 or more consecutive nucleotides of a nucleic acid of the invention.

[00136] Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences corresponding to one or more predictive markers of the invention. The probe comprises a label group attached thereto, *e.g.*, a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as part of a diagnostic test kit for identifying cells or tissues which express the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, *e.g.*, detecting mRNA levels or determining whether a gene encoding the protein has been mutated or deleted.

[00137] In addition to the nucleotide sequences described in the database records described herein, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequence can exist within a population (*e.g.*, the human population). Such genetic polymorphisms can exist among individuals within a population due to natural allelic variation. An allele is one of a group of genes which occur alternatively at a given genetic locus. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist that may affect the overall expression level of that gene (*e.g.*, by affecting regulation or degradation).

[00138] As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a polypeptide corresponding to a marker of the invention, including, e.g., sequences which differ, due to degeneracy of the genetic code, from the nucleotide sequence of nucleic acids encoding a protein which corresponds to a marker of the invention, and thus encode the same protein..

[00139] As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

[00140] The present invention encompasses antisense nucleic acid molecules, *i.e.*, molecules which are complementary to a sense nucleic acid of the invention, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule corresponding to

a marker of the invention or complementary to an mRNA sequence corresponding to a marker of the invention. Accordingly, an antisense nucleic acid of the invention can hydrogen bond to (*i.e.* anneal with) a sense nucleic acid of the invention. The antisense nucleic acid can be complementary to an entire coding strand, or to only a portion thereof, *e.g.*, all or part of the protein coding region (or open reading frame). An antisense nucleic acid molecule can also be antisense to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding a polypeptide of the invention. The non-coding regions ("5' and 3' untranslated regions") are the 5' and 3' sequences which flank the coding region and are not translated into amino acids.

[00141] An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 or more nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2- methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been sub-cloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an

antisense orientation to a target nucleic acid of interest, described further in the following subsection).

[00142] In various embodiments, the nucleic acid molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup *et al.*, 1996, *Bioorganic & Medicinal Chemistry* 4(1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup *et al.* (1996), *supra*; Perry-O'Keefe *et al.* (1996) *Proc. Natl. Acad. Sci. USA* 93:14670-675.

[00143] PNAs can be used in therapeutic and diagnostic applications. For example, PNAs can be used, *e.g.*, in the analysis of single base pair mutations in a gene by, *e.g.*, PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, *e.g.*, S1 nucleases (Hyrup (1996), *supra*; or as probes or primers for DNA sequence and hybridization (Hyrup, 1996, *supra*; Perry-O'Keefe *et al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:14670-675).

[00144] In another aspect, PNAs can be modified, *e.g.*, to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated which can combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, *e.g.*, RNASE H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup, 1996, *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), *supra,* and Finn *et al.* (1996) *Nucleic Acids Res.* 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine

phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag *et al.*, 1989, *Nucleic Acids Res.* 17:5973-88). PNA monomers are then coupled in a step-wise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn *et al.*, 1996, *Nucleic Acids Res.* 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser *et al.*, 1975, *Bioorganic Med. Chem. Lett.* 5:1119-11124).

[00145] In other embodiments, the oligonucleotide can include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre *et al.*, 1987, *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. WO 88/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, 1988, *Bio/Techniques* 6:958-976) or intercalating agents (see, *e.g.*, Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

[00146] The invention also includes molecular beacon nucleic acids having at least one region which is complementary to a marker of the invention, such that the molecular beacon is useful for quantitating the presence of the predictive marker of the invention in a sample. A "molecular beacon" nucleic acid is a nucleic acid comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid are not annealed with one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acids are described, for example, in U.S. Patent 5,876,930.

[00147] Vectors, preferably expression vectors, containing a nucleic acid encoding a polypeptide corresponding to a predictive marker of the invention can be used for production of nucleic acid and proteins corresponding to predictive markers of the invention; as well as for production of compositions relating to the predictive markers. Useful vectors further comprise promoter and/or regulatory sequences for effective expression of the nucleic acid and/or protein corresponding to the predictive marker of

interest. In certain instances, promoters can include constitutive promoter/regulatory sequences, inducible promoter/regulatory sequences, tissue specific promoter/regulatory sequences, or the natural endogenous promoter/regulatory sequences corresponding to the predictive marker of interest, as required. Various expression vectors are well known in the art and can be adapted to suit the particular system for expression. For example, recombinant expression vectors of the invention can be designed for expression of a polypeptide corresponding to a marker of the invention in prokaryotic (*e.g.*, *E. coli*) or eukaryotic cells (*e.g.*, insect cells {using baculovirus expression vectors}, yeast cells or mammalian cells). Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

[00148] As used herein, the term "promoter/regulatory sequence" means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue-specific manner.

[00149] A "constitutive" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell under most or all physiological conditions of the cell.

[00150] An "inducible" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only when an inducer which corresponds to the promoter is present in the cell.

[00151] A "tissue-specific" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

[00152] Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such

terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein. A host cell can be any prokaryotic (*e.g.*, *E. coli*) or eukaryotic cell (*e.g.*, insect cells, yeast or mammalian cells).

[00153] Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

[00154] A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce a polypeptide corresponding to a marker of the invention. Accordingly, the invention further provides methods for producing a polypeptide corresponding to a marker of the invention using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding a polypeptide of the invention has been introduced) in a suitable medium such that the marker is produced. In another embodiment, the method further comprises isolating the marker polypeptide from the medium or the host cell.

Isolated Proteins and Antibodies

[00155] One aspect of the invention pertains to isolated proteins which correspond to predictive markers of the invention, and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a polypeptide corresponding to a predictive marker of the invention. Polypeptides for use in the invention can be isolated, purified, or produced using the gene identification information provided herein in combination with routine molecular biology, protein purification and recombinant DNA techniques well known in the art.

[00156] Biologically active portions of a polypeptide corresponding to a marker of the invention include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the protein corresponding to the predictive marker,

which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding protein. A biologically active portion of a protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of a polypeptide of the invention.

[00157] Preferred polypeptides have the amino acid sequence listed in the one of the GenBank and NUC database records described herein. Other useful proteins are substantially identical (*e.g.*, at least about 50%, preferably 70%, 80%, 90%, 95%, or 99%) to one of these sequences and retain the functional activity of the protein of the corresponding naturally-occurring protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

[00158] The determination of percent identity between two sequences can be accomplished using a mathematical algorithm determining the number of identical positions shared between two sequences. Determination can be carried out using any known method in the art for comparison of identity and similarity. Examples of methods used can include for example, a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See http://www.ncbi.nlm.nih.gov. Another example of a mathematical algorithm utilized for the

comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85:2444-2448. When using the FASTA algorithm for comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a *k*-tuple value of 2. The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

[00159] The invention also provides chimeric or fusion proteins corresponding to a marker of the invention. As used herein, a "chimeric protein" or "fusion protein" comprises all or part (preferably a biologically active part) of a polypeptide corresponding to a marker of the invention operably linked to a heterologous polypeptide (*i.e.*, a polypeptide other than the polypeptide corresponding to the marker). Within the fusion protein, the term "operably linked" is intended to indicate that the polypeptide of the invention and the heterologous polypeptide are fused in-frame to each other. The heterologous polypeptide can be fused to the amino-terminus or the carboxyl-terminus of the polypeptide of the invention. Useful fusion proteins can include GST, c-myc, FLAG, HA, and any other well known heterologous tag for use in fusion protein production. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

[00160] In addition, fusion proteins can include a signal sequence from another protein such as gp67, melittin, human placental alkaline phosphatase, and phoA. In yet another aspect, the fusion protein is an immunoglobulin fusion protein in which all or part of a polypeptide corresponding to a predictive marker of the invention is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies directed against a polypeptide of the invention in a subject, to purify ligands and in screening assays to identify molecules which inhibit the interaction of receptors with ligands.

[00161] An isolated polypeptide corresponding to a predictive marker of the invention, or a fragment thereof, can be used as an immunogen to generate antibodies using standard techniques for polyclonal and monoclonal antibody preparation. For example, an

immunogen typically is used to prepare antibodies by immunizing a suitable (*i.e.* immunocompetent) subject such as a rabbit, goat, mouse, or other mammal or vertebrate. An appropriate immunogenic preparation can contain, for example, recombinantly-expressed or chemically-synthesized polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or a similar immunostimulatory agent.

[00162] Accordingly, another aspect of the invention pertains to antibodies directed against a polypeptide of the invention. The terms "antibody" and "antibody substance" as used interchangeably herein refer to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site which specifically binds an antigen, such as a polypeptide of the invention, *e.g.*, an epitope of a polypeptide of the invention. A molecule which specifically binds to a given polypeptide of the invention is a molecule which binds the polypeptide, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the polypeptide. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and $F(ab')_2$ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies.

[00163] Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a polypeptide of the invention as an immunogen. Preferred polyclonal antibody compositions are ones that have been selected for antibodies directed against a predictive marker or markers of the invention. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules can be harvested or isolated from the subject (*e.g.*, from the blood or serum of the subject) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction.

[00164] Alternatively, antibodies specific for a protein or polypeptide of the invention can be selected or (*e.g.*, partially purified) or purified by, *e.g.*, affinity chromatography to obtain substantially purified and purified antibody. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those of the desired protein or polypeptide of the invention, and preferably at most 20%, yet more

preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein or polypeptide of the invention.

[00165] Additionally, monoclonal antibodies directed to the predictive markers can be prepared for use in the methods of the present invention. Methods for generation of monoclonal antibodies are well known in the art and can be produced using any method. For example, at an appropriate time after immunization, *e.g.*, when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell hybridoma technique (see Kozbor *et al.*, 1983, *Immunol. Today* 4:72), the EBV-hybridoma technique (see Cole *et al.*, pp. 77-96 In *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., 1985) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology,* Coligan *et al.* ed., John Wiley & Sons, New York, 1994). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, *e.g.*, using a standard ELISA assay.

[00166] Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, *e.g.,* Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Humanized antibodies are antibody molecules from non-human species having one or more complementarily determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, *e.g.,* Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO

86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521- 3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Cancer Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; and Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559); Morrison (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

[00167] Human antibodies can be produced, for example, using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of a polypeptide corresponding to a marker of the invention. Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995) *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, *e.g.*, U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[00168] Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, *e.g.*, a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope (Jespers *et al.,* 1994, *Bio/technology* 12:899-903).

[00169] An antibody directed against a polypeptide corresponding to a predictive marker of the invention (*e.g.*, a monoclonal antibody) can be used to detect the predictive marker (*e.g.*, in a cellular sample) in order to evaluate the level and pattern of expression of the predictive marker. The antibodies can also be used diagnostically to monitor protein

levels in tissues or body fluids (*e.g.* in an tumor sample) as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

[00170] Further, an antibody (or fragment thereof) can be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

[00171] Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in

Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982).

[00172] Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

[00173] Accordingly, in one aspect, the invention provides substantially purified antibodies or fragments thereof, and non-human antibodies or fragments thereof, which antibodies or fragments specifically bind to a polypeptide comprising an amino acid sequence encoded by a predictive marker identified herein. In various embodiments, the substantially purified antibodies of the invention, or fragments thereof, can be human, non-human, chimeric and/or humanized antibodies.

[00174] In another aspect, the invention provides non-human antibodies or fragments thereof, which antibodies or fragments specifically bind to a polypeptide comprising an amino acid sequence which is encoded by a nucleic acid molecule of a predictive marker of the invention. Such non-human antibodies can be goat, mouse, sheep, horse, chicken, rabbit, or rat antibodies. Alternatively, the non-human antibodies of the invention can be chimeric and/or humanized antibodies. In addition, the non-human antibodies of the invention can be polyclonal antibodies or monoclonal antibodies.

[00175] In still a further aspect, the invention provides monoclonal antibodies or fragments thereof, which antibodies or fragments specifically bind to a polypeptide comprising an amino acid sequence selected from the group consisting of the amino acid sequences of the present invention, an amino acid sequence encoded by the cDNA of the present invention, a fragment of at least 15 amino acid residues of an amino acid sequence of the present invention, an amino acid sequence which is at least 95% identical to an amino acid sequence of the present invention (wherein the percent identity is determined using the ALIGN program of the GCG software package with a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4) and an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule consisting of the nucleic acid molecules of the present invention, or a complement thereof, under conditions

of hybridization of 6X SSC at 45°C and washing in 0.2 X SSC, 0.1% SDS at 65°C. The monoclonal antibodies can be human, humanized, chimeric and/or non-human antibodies.

[00176] The substantially purified antibodies or fragments thereof may specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain or cytoplasmic membrane of a polypeptide of the invention. In a particularly preferred embodiment, the substantially purified antibodies or fragments thereof, the non-human antibodies or fragments thereof, and/or the monoclonal antibodies or fragments thereof, of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of the present invention.

[00177] The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the invention is a diagnostic composition comprising an antibody of the invention and a pharmaceutically acceptable carrier. In preferred embodiments, the diagnostic composition contains an antibody of the invention, a detectable moiety, and a pharmaceutically acceptable carrier.

Screening Assays

[00178] The invention also provides methods (also referred to herein as "screening assays") for identifying modulators, *i.e.,* candidate or test compounds or agents (*e.g.,* peptides, peptidomimetics, peptoids, small molecules or other drugs) which (a) bind to the marker, or (b) have a modulatory (*e.g.,* stimulatory or inhibitory) effect on the activity of the marker or, more specifically, (c) have a modulatory effect on the interactions of the marker with one or more of its natural substrates (*e.g.,* peptide, protein, hormone, co-factor, or nucleic acid), or (d) have a modulatory effect on the expression of the marker. Such assays typically comprise a reaction between the marker and one or more assay components. The other components may be either the test compound itself, or a combination of test compound and a natural binding partner of the marker.

[00179] Test compounds of the present invention may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. Test compounds may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see,

e.g., Zuckermann *et al.*, 1994, *J. Med. Chem.* 37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

[00180] Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

[00181] Libraries of compounds may be presented in solution (*e.g.*, Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria and/or spores, (Ladner, USP 5,223,409), plasmids (Cull *et al*, 1992, *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla *et al*, 1990, *Proc. Natl. Acad. Sci.* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; Ladner, *supra.*).

[00182] In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a marker or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to a marker or biologically active portion thereof. Determining the ability of the test compound to directly bind to a marker can be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound to the marker can be determined by detecting the labeled marker compound in a complex. For example, compounds (*e.g.*, marker substrates) can be labeled with ^{125}I, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, assay components can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

[00183] In another embodiment, the invention provides assays for screening candidate or test compounds which modulate the activity of a marker or a biologically active portion thereof. In all likelihood, the marker can, *in vivo*, interact with one or more molecules, such as but not limited to, peptides, proteins, hormones, cofactors and nucleic acids. For the purposes of this discussion, such cellular and extracellular molecules are referred to herein as "binding partners" or marker "substrate". One necessary embodiment of the invention in order to facilitate such screening is the use of the marker to identify its natural *in vivo* binding partners. Many of the known binding partners or substrates of the identified predictive markers are either known in the art, or can be identified using standard methodologies known in the art (e.g., two hybrid screening, etc.).

[00184] In a further embodiment, assays may be devised through the use of the invention for the purpose of identifying compounds which modulate (*e.g.,* affect either positively or negatively) interactions between a marker and its substrates and/or binding partners. Such compounds can include, but are not limited to, molecules such as antibodies, peptides, hormones, oligonucleotides, nucleic acids, and analogs thereof. Such compounds may also be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. The preferred assay components for use in this embodiment is an predictive marker identified herein, the known binding partner and/or substrate of same, and the test compound. Test compounds can be supplied from any source.

[00185] The basic principle of the assay systems used to identify compounds that interfere with the interaction between the marker and its binding partner involves preparing a reaction mixture containing the marker and its binding partner under conditions and for a time sufficient to allow the two products to interact and bind, thus forming a complex. In order to test an agent for inhibitory activity, the reaction mixture is prepared in the presence and absence of the test compound. The test compound can be initially included in the reaction mixture, or can be added at a time subsequent to the addition of the marker and its binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The formation of any complexes between the marker and its binding partner is then detected. The formation of a complex in the control reaction, but less or no such formation in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the marker and its binding partner. Conversely, the formation of more complex in the presence of compound than in the control reaction indicates that the compound may enhance interaction of the marker and its binding partner.

[00186] The assay for compounds that interfere with the interaction of the marker with its binding partner may be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the marker or its binding partner onto a solid phase and detecting complexes anchored to the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds that interfere with the interaction between the markers and the binding partners (*e.g.,* by competition) can be identified by conducting the reaction in the presence of the test substance, *i.e.,* by adding the test substance to the reaction mixture prior to or simultaneously with the marker and its interactive binding partner. Alternatively, test compounds that disrupt preformed complexes, *e.g.,* compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are briefly described below.

[00187] In a heterogeneous assay system, either the marker or its binding partner is anchored onto a solid surface or matrix, while the other corresponding non-anchored component may be labeled, either directly or indirectly. In practice, microtitre plates are often utilized for this approach. The anchored species can be immobilized by a number of methods, either non-covalent or covalent, that are typically well known to one who practices the art. Non-covalent attachment can often be accomplished simply by coating the solid surface with a solution of the marker or its binding partner and drying. Alternatively, an immobilized antibody specific for the assay component to be anchored can be used for this purpose. Such surfaces can often be prepared in advance and stored.

[00188] In related embodiments, a fusion protein can be provided which adds a domain that allows one or both of the assay components to be anchored to a matrix. For example, glutathione-S-transferase/marker fusion proteins or glutathione-S-transferase/binding partner can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, which are then combined with the test compound or the test compound and either the non-adsorbed marker or its binding partner, and the mixture incubated under conditions conducive to complex formation (*e.g.,* physiological conditions). Following incubation, the beads or microtiter plate wells are washed to remove any unbound assay components, the immobilized complex

assessed either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of marker binding or activity determined using standard techniques.

[00189] Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a marker or a marker binding partner can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated marker protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.,* biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the protein-immobilized surfaces can be prepared in advance and stored.

[00190] In order to conduct the assay, the corresponding partner of the immobilized assay component is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted assay components are removed (*e.g.,* by washing) and any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the non-immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; *e.g.*, using a labeled antibody specific for the initially non-immobilized species (the antibody, in turn, can be directly labeled or indirectly labeled with, *e.g.*, a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which modulate (inhibit or enhance) complex formation or which disrupt preformed complexes can be detected.

[00191] In an alternate embodiment of the invention, a homogeneous assay may be used. This is typically a reaction, analogous to those mentioned above, which is conducted in a liquid phase in the presence or absence of the test compound. The formed complexes are then separated from unreacted components, and the amount of complex formed is determined. As mentioned for heterogeneous assay systems, the order of addition of reactants to the liquid phase can yield information about which test compounds modulate (inhibit or enhance) complex formation and which disrupt preformed complexes.

[00192] In such a homogeneous assay, the reaction products may be separated from unreacted assay components by any of a number of standard techniques, including but not

limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, complexes of molecules may be separated from uncomplexed molecules through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., *Trends Biochem Sci* 1993 Aug;18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the complex as compared to the uncomplexed molecules may be exploited to differentially separate the complex from the remaining individual reactants, for example through the use of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, *e.g.,* Heegaard, 1998, *J Mol. Recognit.* 11:141-148; Hage and Tweed, 1997, *J. Chromatogr. B. Biomed. Sci. Appl.,* 699:499-525). Gel electrophoresis may also be employed to separate complexed molecules from unbound species (see, *e.g.,* Ausubel *et al* (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, nondenaturing gels in the absence of reducing agent are typically preferred, but conditions appropriate to the particular interactants will be well known to one skilled in the art. Immunoprecipitation is another common technique utilized for the isolation of a protein-protein complex from solution (see, *e.g.,* Ausubel *et al* (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, all proteins binding to an antibody specific to one of the binding molecules are precipitated from solution by conjugating the antibody to a polymer bead that may be readily collected by centrifugation. The bound assay components are released from the beads (through a specific proteolysis event or other technique well known in the art which will not disturb the protein-protein interaction in the complex), and a second immunoprecipitation step is performed, this time utilizing antibodies specific for the correspondingly different interacting assay component. In this manner, only formed complexes should remain attached to the beads. Variations in complex formation in both the presence and the absence of a test compound can be compared, thus offering information

about the ability of the compound to modulate interactions between the marker and its binding partner.

[00193] Also within the scope of the present invention are methods for direct detection of interactions between the marker and its natural binding partner and/or a test compound in a homogeneous or heterogeneous assay system without further sample manipulation. For example, the technique of fluorescence energy transfer may be utilized (see, *e.g.,* Lakowicz *et al,* U.S. Patent No. 5,631,169; Stavrianopoulos *et al,* U.S. Patent No. 4,868,103). Generally, this technique involves the addition of a fluorophore label on a first 'donor' molecule (*e.g.,* marker or test compound) such that its emitted fluorescent energy will be absorbed by a fluorescent label on a second, 'acceptor' molecule (*e.g.,* marker or test compound), which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (*e.g.,* using a fluorimeter). A test substance which either enhances or hinders participation of one of the species in the preformed complex will result in the generation of a signal variant to that of background. In this way, test substances that modulate interactions between a marker and its binding partner can be identified in controlled assays.

[00194] In another embodiment, modulators of marker expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of mRNA or protein, corresponding to a marker in the cell, is determined. The level of expression of mRNA or protein in the presence of the candidate compound is compared to the level of expression of mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of marker expression based on this comparison. For example, when expression of marker mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of marker mRNA or protein expression. Conversely, when expression of marker mRNA or protein is less (statistically

significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of marker mRNA or protein expression. The level of marker mRNA or protein expression in the cells can be determined by methods described herein for detecting marker mRNA or protein.

[00195] Still futher, in cell based assays, where a cell expressing a predictive marker of interest is used for screening therapeutic candidate agents, the activity or viability of the cell is monitored to determine the ability of the test compound to alter the activity of the predictive marker or markers. Such assays are carried in tandem with a control assay utilizing similar or identical cell lines which do not express the predictive marker or markers of interest, in order to determine specificity of the action of the test compound.

[00196] In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a marker protein can be further confirmed *in vivo*, *e.g.*, in a whole animal model for cellular transformation and/or tumorigenesis.

[00197] This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, an marker modulating agent, an antisense marker nucleic acid molecule, an marker-specific antibody, or an marker-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent.

SPECIFIC EXAMPLES

Treatment Dosage and Administration

Drug Supply and Storage

[00198] Bortezomib for injection (VELCADE™ Millennium Pharmaceuticals, Inc., Cambridge, MA), a sterile lyophilized powder for reconstitution, was supplied in vials containing 2.5 mg bortezomib and 25 mg mannitol USP. Each vial was reconstituted with 2.5 mL of normal (0.9%) saline, Sodium Chloride Injection USP, such that the reconstituted solution contained bortezomib at a concentration of 1 mg/mL. The reconstituted solution

was clear and colorless with a final pH between 5 and 6. Vials containing lyophilized bortezomib for Injection were stored refrigerated at 2 to 8°C.

TABLE B Drug Information

Chemical Name	N-Pyrazinecarbonyl-L-phenylalanine-L-leucineboronic acid
Research Name	MLN341 or PS-341
Generic Name	bortezomib
Proprietary Name	VELCADE™
CAS Registry Number	179324-69-7
U.S. Patent Number	5,780,454
Classification	Proteasome Inhibitor
Molecular Formula	$C_{19}H_{25}BN_4O_4$
Molecular Weight	384.25
Structure	Boronic acid derivative of a leucine phenylalanine dipeptide

An Open-Label Phase II Study of Bortezomib in Patients with Myeloma Who Have Relapsed Following Front-line Therapy and are Refractory to their Most Recent Therapy

Pharmacodynamic/pharmacogenomic/pharmacokinetic data collected

[00199] A multicenter, open-label, non-randomized Phase 2 trial was conducted, wherein enrolled were patients with relapsed myeloma that was refractory to therapy. Patients were treated with 1.3 mg of bortezomib per square meter of body surface area, twice weekly for two weeks, followed by one week without treatment, for up to eight cycles (24 weeks).

[00200] The following evaluations were conducted to assess the pharmacodynamics and pharmacogenomics of bortezomib:.

[00201] Proteasome inhibition assay (blood for this *ex vivo* assay was collected before and one hour after dosing on Day 1 and Day 11 of Cycles 1, 7, and, if applicable, the cycle in which dexamethasone was started and one hour after dosing on Day 11 of Cycle 8). Some patients had an additional sample collected for the proteasome inhibition assay at 24 hours after dosing on Day 1, Cycle 1.

[00202] Pharmacogenomic data (blood and bone marrow samples for evaluation of the expression of global mRNA levels; these procedures were conducted only in patients who consented to participate via a separate consent form).

[00203] Population pharmacokinetics (blood for determination of population pharmacokinetics was collected from all patients before and one to six hours after study drug administration on Day 1, Cycle 1, and before and one to six hours after study drug administration on Day 11 of Cycles 1, 2, 7, and 8 and, if applicable, the cycle in which dexamethasone was started). Pre-dose blood samples were collected at the same time as those for clinical laboratory evaluations.

[00204] Individual pharmacokinetics: blood for determination of plasma bortezomib levels was collected immediately before and at 2, 5, 10, 15, 30, 60, and 120 minutes and 24 hours after bortezomib administration on Day 1, Cycle 1.

Statistical procedures

[00205] Statistical analysis focused on the need to estimate response rates within specified limits of accuracy in order to determine if either of the two dose levels 1.0 or 1.3 mg/m^2/dose alone or in combination with dexamethasone are sufficiently efficacious to warrant further clinical study. This study was noncomparative in nature; therefore efficacy comparisons between the two doses of bortezomib were not performed. In addition, this study provided safety data that helped to characterize the potential toxicity of treatment at the two evaluated dose levels for up to eight cycles of therapy.

[00206] Summary tabulations were presented that displayed the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The categories for summarization were the two assigned dose groups.

[00207] A formal statistical analysis plan was developed and finalized prior to database lock. The primary efficacy analyses were performed on the intent-to-treat (ITT) population. The primary efficacy analysis were performed on the rates of responders, where a responder was defined as a CR, PR, or MR using the criteria prospectively established in Table C. Two-sided 90% confidence limits on proportions of responders in each dose group were established, corresponding to a 95% one-sided lower limit.

Table C Disease Response Criteria[1]

Response	Criteria for response
Complete response (CR)[2]	Requires all of the following: Disappearance of the original monoclonal protein from the blood and urine on at least two determinations for a minimum of six weeks by immunofixation studies. < 5% plasma cells in the bone marrow on at least two determinations

Table C Disease Response Criteria[1]

Response	Criteria for response
	for a minimum of six weeks. No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response). Disappearance of soft tissue plasmacytomas for at least six weeks.
Partial response (PR)[3]	PR includes patients in whom some, but not all, criteria for CR are fulfilled providing the remaining criteria satisfy the requirements for PR. Requires all of the following: ≥50% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart. If present, reduction in 24-hour urinary light chain excretion by either ≥90% or to < 200 mg for at least two determinations six weeks apart. ≥ 50% reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examination) for at least six weeks. No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
Minimal response (MR)	MR includes patients in whom some, but not all, criteria for PR are fulfilled providing the remaining criteria satisfy the requirements for MR. Requires all of the following: ≥25% to ≤ 49% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart. If present, a 50 to 89% reduction in 24-hour light chain excretion, which still exceeds 200 mg/24 h, for at least two determinations six weeks apart. For patients with non-secretory myeloma only, a 25 to 49% reduction in plasma cells in the bone marrow for a minimum of six weeks. 25-49% reduction in the size of plasmacytomas (by clinical or radiographic examination) for at least six weeks. No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
No change (NC)	Not meeting the criteria for MR or PD.
Progressive disease (PD) (for patients not in CR)	Requires one or more of the following: >25% increase in the level of serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/L and confirmed on a repeat investigation. >25% increase in 24-hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed on a repeat investigation. >25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%. Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas. Development of new bone lesions or soft tissue plasmacytomas (not including compression fracture). Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L not attributable to any other cause).
Relapse from CR	Requires at least one of the following: Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis confirmed by at least one follow-up and excluding oligoclonal immune reconstitution.

Table C Disease Response Criteria[1]

Response	Criteria for response
	≥5% plasma cells in the bone marrow aspirate or biopsy. Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (not including compression fracture). Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L not attributable to any other cause).

Based on the criteria reported by Kraut *et al.*, *J. Clin. Oncol.* 16(2): 589-592 (1998) and Blade *et al.*, *Br. J. Haematol.* 102(5): 1115-1123 (1998). In patients with CR, bone marrow was analyzed using PCR for verification of CR at the molecular level. Patients who met all criteria for PR but who exhibit a ≥75% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart were termed in 'Remission' (R).

[00208] Quality of Life assessment was analyzed to determine if response to therapy was accompanied by measurable improvement in quality of life. Analysis was performed on summary scores as well as individual items, with specific analytical methods outlined in a formal statistical analysis plan developed prior to database lock.

[00209] Pharmacodynamic data (20S proteasome) were descriptively analyzed in order to characterize the degree of proteasome inhibition, and to investigate any correlation between degree of inhibition and therapeutic response and toxicity.

[00210] For those patients who participated in the pharmacogenomic portion of the study, correlation between RNA expression levels and response to therapy were evaluated descriptively. In addition, duration of response, time to disease progression, and overall patient survival may be analyzed using RNA expression as a factor.

[00211] A total of 202 patients were enrolled in the study. The overall response rate to PS-341 alone was 35% (CR+PR rate of 27%) prior to any patients receiving added dexamethasone for non-optimal response. These patients had all received at least two prior treatment regimens for their disease and their disease had progressed on their most recent therapy. This patient population has a very poor prognosis and no available standard therapy. Karnofsky Performance Status (KPS) was ≤70 in 25% of patients, and Durie-Salmon stage was reported as IIA or IIIB in 79% of patients. Approximately 39% of the patients had β_2 microglobulin ≥4 mg/L at Baseline, with 22% of patients having this indicator of disease severity ≥6 mg/L. The majority of the patients had relapsed after all conventional, high-dose, and novel therapies, with 74% progressing despite prior treatment with thalidomide.

[00212] The dose of 1.3 mg/m^2 twice weekly for two weeks followed by a 10-day rest was well tolerated. Over 80% of the 78 patients completed 2 or more cycles of treatment, 62% completed 4 or more cycles, and 27% completed 8 cycles.

[00213] The Independent Review Committee (IRC) evaluation of confirmed response to treatment with bortezomib alone is provided in Table D; further categorization of response for those patients who experienced partial remission is provided in Table E. This independent panel panel of three medical oncologists reviewed all data for 193 evaluable patients in the trial and assigned response using Blade criteria (Table C). The IRC determined that 35% of these 193 patients with relapsed/refractory multiple myeloma had a response to treatment (CR + PR + MR) with bortezomib alone, with 53 (27%) of the 193 patients experiencing a complete or partial remission to therapy and an additional 14 patients with a minimal response. An additional 46 (24%) of patients had evidence for stable disease (NC, no change) in response to bortezomib alone, which reflects an improvement in status for these patients who were progressing at the time of study entry. Based on the IRC assessment, 38 (20%) of the 193 patients had progressive disease and an additional 42 patients (22%) were considered not evaluable for response by the IRC. These data have been published. See Richardson PG, et al., *New Eng. J. Med.*;348: 2609-17 (2003).

[00214] All pharmacogenomic analyses relied on the Independent Review Committee's judgement of response category.

Table D: Summary of IRC Confirmed Response to Treatment with bortezomib Alone (N = 193)

Confirmed Response Category	Response to bortezomib[a]
Complete + Partial + Minor Responses	67 (35%)
Complete + Partial Remissions	53 (27%)
Complete + Near Complete Remissions (NCR)	19 (10%)
Complete Remission (CR)	19 (4%)
Partial Remission (PR)	34 (23%)
Minor Response (MR)	14 (5%)
No Change	46 (27%)
Progressive Disease	38 (20%)
Not Evaluable	42 (22%)

a Response to treatment while patients were receiving bortezomib alone. (N = 193)

Identification Of Responsive and Non-Predictive markers

[00215] 44 multiple myeloma patients had high quality gene expression data.

[00216] Candidate markers that are correlated with the outcome of multiple myeloma patients to a proteasome inhibition (e.g., bortezomib) therapy were selected by using a combination of marker ranking algorithms. Supervised learning and feature selection algorithms were then used to identify the markers of the present invention.

Data Analysis

[00217] A data set, comprised of 44 discovery samples, was classified as responders (N_R=17), stable disease (N_S = 12), or progressive disease (N_P = 15), based on the assignments of the IRC. For marker identification, the three response classes were further grouped into responders (N_R=17) vs non-responders (N_{NR} = 27), or refractory/progressive disease (N_P = 15) vs others (N = 29). For each sample, 44,928 gene transcripts (Affymetrix probe sets) were profiled on the two Affymetrix U133 microarrays according to manufacturer's directions. Total RNA was isolated from homogenized tissue by TriazolTM (Life Technologies, Inc.) following the manufacturer's recommendations. RNA was stored at 80 °C in diethyl pyrocarbonate-treated deionized water. Detailed methods for labeling the samples and subsequent hybridization to the arrays are available from Affymetrix (Santa Clara, CA). Briefly, 5.0 μg of total RNA was converted to double-stranded cDNA (Superscript; Life Technologies, Inc.) priming the first-strand synthesis with a T7-(dT)24 primer containing a T7 polymerase promoter (Affymetrix Inc.). All of the double-stranded cDNA was subsequently used as a template to generate biotinylated cRNA using the incorporated T7 promoter sequence in an in vitro transcription system (Megascript kit; Ambion and Bio-11-CTP and Bio-16-UTP; Enzo). Control oligonucleotides and spikes were added to 10 μg of cRNA, which was then hybridized to U133 oligonucleotide arrays for 16 h at 45 °C with constant rotation. The arrays were then washed and stained on an Affymetrix fluidics station using the EUKGE-WS1 protocol and scanned on an Affymetrix GeneArray scanner.

Normalization and Logarithmic Transformation.

[00218] Expression values for all markers on each microarray were normalized to a trimmed mean of 150. Expression values were determined using MAS5 gene expression analysis data processing software (Affymetrix, Santa Clara, CA). These values will be referred to as the "normalized expression" in the remainder of this section. In a further processing step, each normalized expression value was divided by 150, and added to 1. The natural logarithm was taken of the resulting number, and this value will be referred to as the "log expression" in the remainder of this section.

Single Marker Selection.

[00219] Single gene transcripts that appear associated with sample classes can be identified using the feature ranking and filtering methodology described below. Single

marker identification of Predictive Markers using the methodology described herein are set forth in Table 1 Table 2 and Table 3.

Model Selection.

[00220] A set of one or more gene transcripts that together classify samples into sensitive and resistant groups (or responsive and non-responsive), in the context if a particular classifier algorithm, is referred to as a "model." The gene transcripts are referred to as "features." Determining which combination of gene transcript(s) best classifies samples into sensitive and resistant groups is referred to as "model selection." The following section describes the process of how the models of the present invention were identified. Exemplary models are set forth in Table 4, Table 5, and Table 6. The methods provided herein along with the single marker identification or Predictive markers can be used to identify additional models comprising markers of the invention.

Summary Of The Data Provided In The Tables

[00221] The following terms are used throughout the Tables:

"No." or "Number" corresponds to an identification number for the markers.

"Probeset ID" corresponds to the Affymetrix (Santa Clara, CA) identifier from the Human Genome U133 set oligonucleotide arrays which were used;

"Sequence Derived from" or "Genbank" or "RefSeq" corresponds to the public database accession information for the markers.

"RefSeq" corresponds to the Reference Sequence Nucleic Accession Number;

"Genbank" corresponds to the GenBank accession number assigned to the particular sequence. All referenced GenBank sequences are expressly incorporated herein by reference;

"Title" corresponds to a common description, where available;

"Gene symbol" corresponds to a symbol the gene is commonly known by;

"Unigene" corresponds to the unique gene identifier;

"Rank____" corresponds to the process of determining which individual markers may be used in combination to group or classify a sample, for example, as responsive(R) or non-responsive(NR). Rank and the relative scoring method used for various ranking is indicated, as is the lowest rank score identified among all the methods for each of the predictive markers. Four different feature selection methods were utilized for determining the best classifier: (1) Signal-to-Noise Ratio ("SNR"), (2) Class-Based

Threshold ("CBT"), (3) Pooled Fold Change ("PFC"), and (4) the Wilcoxon Rank-Sum Test;

Additional titles correspond to scored and parameters used in each of the methods described in the following exemplification, including "Hazard," "Decision Boundary," "Weight," "Vote Weight," "Vote," "Confidence," "Expression," "Gene Expression," "Log Gene Expression," "Normalized Expression," and "Normalization Factor;" "Supplemental Annotation" and "Biological Category" correspond to additional characterization and categorization not set forth in the title;

For Table 8, cell lines were designated as Sensitive "S" or Resistant "R;" and "Ratio of Sensitive/Resistant" indicates relative expression of marker indicated.

Feature ranking and filtering

[00222] The first step in model selection is to filter the 44,928 features down to a smaller number which show a correspondence with the sample classifications. Filtering involves first ranking the features by a scoring method, and then taking only the highest ranking features for forther analysis. The filtering algorithms used in the present invention were: (1) Signal-to-Noise Ratio ("SNR"), (2) Class-Based Threshold ("CBT"), (3) Pooled Fold Change ("PFC"), and (4) the Wilcoxon Rank-Sum Test. In preferred embodiments, SNR was used to identify genes showing a small but consistent change in levels, and CBT was used to identify genes that were "off" in one class, but "on" in a fraction of the other class.

[00223] SNR is computed from the log expression values as absolute value of the difference in class means divided by the sum of the class standard deviations, and has been used to analyze expression data before; for example, see the definition of P(g,c), a measure of correlation between expression of gene g and class vector c, in Golub et al., "Molecular Classification of Cancer: Class discovery and class prediction by marker expression monitoring," Science, 286:531-537 (1999), the contents of which are incorporated herein by reference. To use SNR for filtering, the features with the top 100 SNR scores were retained and the remainder discarded from consideration.

[00224] CBT is computed from the normalized expression values, and defines one class ("class A") as the "off" class, and the other class ("class B") as the "on" class. In the present studies, the "off" class, class A is Responders; and the "on" class, class B, is Non-Responders. The CBT score may be computed in one of two ways: (1) Threshold each

class B value to the average class A expression value for that feature. CBT is the difference between the average thresholded class B expression and the average class A expression, divided by the standard deviation of the class A expression:

$$CBT = \frac{\frac{1}{N_B}[\sum_{i=1}^{N_B} \max(x_i, \mu_A)] - \mu_A}{\sigma_A}$$

where μ_A is the average class A expression value, σ_A is the standard deviation of the class A expression values, and x_i represent the N_B individual class B expression values. (2) CBT is the percentage of class B samples which exceed a fixed multiple of the maximum (or other percentile value) of expression values in class A. In either method, a constant value may be added to the class A threshold value to compensate for noise. In preferred embodiments, method 1 was utilized, and the top 100 features were selected.

[00225] The Pooled Fold Change ("PFC") method is a measure of differential expression between two groups of samples, arbitrarily designated "control" and "tester." PFC finds genes with higher expression in the tester than in the control samples. The analysis was performed looking at both Responders as "tester" (PFC-R) and Non-Responders as "tester" (PFC-NR). To qualify as having higher expression, tester samples must be above the k^{th} percentile control sample. The fold-change values of tester samples are subjected to a nonlinear transformation that rises to a user-specified asymptote, in order to distinguish moderate levels of fold-change, but not make distinctions between very large fold-changes. The squashed fold-change values of the over-expressed tester samples are averaged to get the POOF score. In particular, PFC for gene g is computed as the average across tester samples of the compressed tester:control ratio R(s,g). For a given tester sample s and gene g, $R(s,g) = C(x_{gs}/(k+x_g^Q))$, where

C(x) is the compression function $C(z) = A(1-e^{-z/A})$ for $z \geq T$, and $C(z) = 0$ for $z<T$, where T is a threshold value no less than 1.0.

A is an upper asymptote on the fold-change value (we used 5),

k is a constant reflecting the additive noise in the data, i.e., the fixed component of the variance in repeated measurements. We derived a value of 30 for this parameter from calibration experiments.

x_{gs} is the expression value of gene g in sample s,

x_g^Q is the Qth percentile of the control samples' expression value.

[00226] Also, a minimum fraction f of the tester samples must have R(s,g) greater than 0; if this does not hold true, then the value of R(s,g) is set to 0.

[00227] We used the following parameters in two runs of this algorithm:

Parameter	Value in run 1	Value in run 2
Q	1.0	0.8
f	0.2	0.4
T	1.25	1.25

[00228] The Wilcoxon Rank-Sum test is a standard statistical technique. See, for example, Conover, W. J. 1980. *Practical Nonparametric Statistics.* 2nd ed. New York: John Wiley & Sons, which is incorporated herein by reference. This test is also known as the Mann-Whitney U test. The goal is to test the null hypothesis that the population distributions corresponding to two random samples are identical against the alternative hypothesis that they are different. Only the rank of the samples' expression values is examined, not the values themselves.

[00229] Markers using the 44,928 probe sets were analyzed for differential expression across the 44 patient samples using the methods described in the above. In particular, we applied PFC (run 1), PFC (run 2), SNR, the Wilcoxon rank-sum test and the Class-Based Threshold as described above. The first three methods were run in each direction, to look for genes up in responders and then up in non-responders. The Wilcoxon rank-sum test was bidirectional and identified genes up in either responders or non-responders. Thus, there were 7 runs of the methods. In each case, the probe sets were sorted based on their score, and ranked. The top 100 ranked probe sets from each method were selected for Table 1. The last column in the table identifies the minimum rank across the methods.

TABLE 1. PREDICTIVE MARKER IDENTIFICATION

No.	Probeset ID	Sequence Derived From	Title	Gene Symbol	Rank NR PFC-1	Rank R PFC-1	Rank NR PFC-2	Rank R PFC-1	Rank NR SNR	Rank R SNR	Rank Wilcoxon rank-sum test	Rank CBT	Minimum rank
1	204298_s_at	NM_002317.1	lysyl oxidase	LOX	44928	44928	44928	44928	44855	74	112	>100	74
2	205884_at	NM_000885.2	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	ITGA4	44928	44928	86	44928	949	43980	2675	>100	86
3	228841_at	AW299250	Homo sapiens cDNA FLJ32429 fis, clone SKMUS2001014.	---	44928	44928	91	44928	95	44834	197	>100	91
4	243366_s_at	AI936034	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	ITGA4	44928	44928	98	44928	1896	43033	6343	>100	98
5	214265_at	AI193623	integrin, alpha 8	ITGA8	14	44928	25	44928	924	44005	4689	16	14
6	203949_at	NM_000250.1	myeloperoxidase	MPO	44928	2	44928	25	44178	751	2599	>100	2
7	207341_at	NM_002777.2	proteinase 3 (serine proteinase, neutrophil, Wegener granulomatosis autoantigen)	PRTN3	44928	4	44928	44928	43054	1875	17751	>100	4
8	203948_s_at	J02694.1	myeloperoxidase	MPO	44928	11	44928	44928	42466	2463	17515	>100	11
9	224461_s_at	BC006121.1	apoptosis-inducing factor (AIF)-homologous mitochondrion-associated inducer of death	AMID	59	44928	44928	44928	360	44569	2121	>100	59
10	206056	X52075	sialophorin (gpL115,	SPN	44928	44928	44928	82	44735	194	304	>100	82

	_x_at		leukosialin, CD43)										
11	203489 _at	NM_0064 27.2	CD27-binding (Siva) protein	SIVA	44928	44928	44928	44928	86	44843	281	>100	86
12	226507 _at	AU15440 8	p21/Cdc42/Rac1-activated kinase 1 (STE20 homolog, yeast)	PAK1	90	44928	44928	44928	974	43955	3521	>100	90
13	216055 _at	AK02292 0.1	platelet-derived growth factor beta polypeptide (simian sarcoma viral (v-sis) oncogene homolog)	PDGFB	44928	44928	44928	44928	44829	100	224	>100	100
14	209942 _x_at	BC000340 .1	melanoma antigen, family A, 3	MAGEA 3	44928	44928	2	44928	217	44712	602	>100	2
15	214612 _x_at	U10691	---	---	44928	44928	4	44928	357	44572	2061	>100	4
16	217969 _at	NM_0132 65.2	melanoma antigen, family D, 1	MAGED 1	8	44928	55	44928	197	44732	2165	4	4
17	215733 _x_at	AJ012833 .1	cancer/testis antigen 2	CTAG2	18	44928	5	44928	922	44007	28547	36	5
18	210546 _x_at	U87459.1	cancer/testis antigen 1	CTAG1	13	44928	7	44928	1278	43651	12645	32	7
19	211674 _x_at	AF038567 .1	cancer/testis antigen 1	CTAG1	21	44928	8	44928	1185	43744	27104	25	8
20	223313 _s_at	BC001207 .1	MAGE-E1 protein	MAGE-E1	44928	44928	44928	12	42615	2314	9805	>100	12
21	210467 _x_at	BC003408 .1	melanoma antigen, family A, 12	MAGEA 12	44928	44928	21	44928	2258	42671	10757	>100	21
22	220057 _at	NM_0204 11.1	G antigen, family D, 2	GAGED 2	44928	44928	24	44928	2785	42144	10634	>100	24
23	236152 _at	AW13533 0	PAGE-5 protein	PAGE-5	40	44928	44928	44928	908	44021	8811	>100	40
24	233831 _at	AI246052	Homo sapiens serologically defined breast cancer antigen	---	44928	44928	44928	44928	44874	55	142	>100	55

			NY-BR-40 mRNA, partial cds										
25	206427_s_at	U06654.1	melan-A	MLANA	44928	44928	44928	44928	44873	56	159	>100	56
26	206218_at	NM_002364.1	melanoma antigen, family B, 2	MAGEB2	63	44928	44928	44928	3637	41292	38186	>100	63
27	203386_at	AI650848	TBC1 domain family, member 4	TBC1D4	44928	44928	44928	44928	44844	85	439	>100	85
28	201457_x_at	AF081496.1	BUB3 budding uninhibited by benzimidazoles 3 homolog (yeast)	BUB3	44928	44928	61	44928	62	44867	113	14	14
29	213348_at	N33167	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	CDKN1C	44928	31	44928	44928	44846	83	147	>100	31
30	204170_s_at	NM_001827.1	CDC28 protein kinase regulatory subunit 2	CKS2	44928	44928	34	44928	464	44465	828	>100	34
31	206205_at	NM_022782.1	M-phase phosphoprotein 9	MPHOSPH9	44928	44928	44928	44928	40	44889	72	>100	40
32	208796_s_at	BC000196.1	cyclin G1	CCNG1	44928	44928	68	44928	250	44679	517	>100	68
33	204460_s_at	AF074717.1	RAD1 homolog (S. pombe)	RAD1	44928	44928	44928	44928	71	44858	128	>100	71
34	224918_x_at	AI220117	microsomal glutathione S-transferase 1	MGST1	28	44928	44928	44928	10617	34312	19002	>100	28
35	205998_x_at	NM_017460.2	cytochrome P450, subfamily IIIA (niphedipine oxidase), polypeptide 4	CYP3A4	44928	44928	44928	44928	44852	77	87	>100	77
36	239476_at	AW152166	Homo sapiens cDNA FLJ36491 fis, clone THYMU2018197.	---	44928	44928	44928	44928	44925	4	9	>100	4
37	211298_s_at	AF116645.1	albumin	ALB	44928	44928	44928	44928	44914	15	95	>100	15
38	216835	AF035299	docking protein 1,	DOK1	44928	44928	44928	44928	44921	8	42	>100	8

	_s_at	.1	62kDa (downstream of tyrosine kinase 1)										
39	213891 _s_at	AI927067	Homo sapiens cDNA FLJ11918 fis, clone HEMBB1000272.	---	44928	44928	44928	20	43578	1351	1063	>100	20
40	212387 _at	AK02198 0.1	Homo sapiens cDNA FLJ11918 fis, clone HEMBB1000272.	---	44928	44928	44928	31	43365	1564	393	>100	31
41	212382 _at	AK02198 0.1	Homo sapiens cDNA FLJ11918 fis, clone HEMBB1000272.	---	44928	40	44928	44928	37843	7086	9000	>100	40
42	203753 _at	NM_0031 99.1	transcription factor 4	TCF4	44928	44928	44928	42	43376	1553	1580	>100	42
43	212386 _at	AK02198 0.1	Homo sapiens cDNA FLJ11918 fis, clone HEMBB1000272.	---	44928	44928	44928	64	42346	2583	1261	>100	64
44	211709 _s_at	BC005810 .1	stem cell growth factor; lymphocyte secreted C-type lectin	SCGF	44928	44928	44928	99	44282	647	1192	>100	99
45	217020 _at	X04014	---	---	44928	44928	44928	44928	44917	12	71	>100	12
46	217786 _at	NM_0061 09.1	SKB1 homolog (S. pombe)	SKB1	44928	44928	44928	44928	34	44895	17	>100	17
47	206109 _at	NM_0001 48.1	fucosyltransferase 1 (galactoside 2-alpha-L-fucosyltransferase, Bombay phenotype included)	FUT1	44928	44928	44928	44928	44907	22	41	>100	22
48	227798 _at	AU14689 1	ESTs	---	44928	44928	23	44928	2520	42409	6771	>100	23
49	208743 _s_at	BC001359 .1	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta	YWHAB	44928	44928	44928	44928	51	44878	100	>100	51

			polypeptide										
50	225239_at	AI355441	ESTs, Moderately similar to hypothetical protein FLJ20958 [Homo sapiens] [H.sapiens]	---	44928	44928	44928	57	44845	84	226	>100	57
51	215551_at	AI073549	estrogen receptor 1	ESR1	44928	44928	44928	44928	44868	61	109	>100	61
52	215067_x_at	AU147942	Homo sapiens cDNA FLJ12333 fis, clone MAMMA1002198, highly similar to THIOREDOXIN PEROXIDASE 1.	---	44928	44928	44928	72	43871	1058	2063	>100	72
53	210993_s_at	U54826.1	MAD, mothers against decapentaplegic homolog 1 (Drosophila)	MADH1	44928	44928	100	44928	3077	41852	5470	>100	100
54	209374_s_at	BC001872.1	immunoglobulin heavy constant mu	IGHM	2	44928	44928	44928	1769	43160	31220	66	2
55	224342_x_at	L14452.1	immunoglobulin lambda locus	IGL@	4	44928	44928	44928	2837	42092	28929	29	4
56	212827_at	X17115.1	immunoglobulin heavy constant mu	IGHM	6	44928	44928	44928	3364	41565	36442	>100	6
57	234366_x_at	AF103591.1	immunoglobulin lambda locus	IGL@	44928	44928	44928	26	30154	14775	21162	>100	26
58	216986_s_at	D78261.1	interferon regulatory factor 4	IRF4	44928	44928	44928	44928	43	44886	129	>100	43
59	205098_at	AI421071	chemokine (C-C motif) receptor 1	CCR1	46	44928	44928	44928	2037	42892	13544	>100	46
60	239237_at	AI798822	ESTs	---	120	44928	79	44928	4324	40605	22488	>100	79
61	205099_s_at	NM_001295.1	chemokine (C-C motif) receptor 1	CCR1	85	44928	44928	44928	3294	41635	13545	>100	85
62	223472	AF071594	Wolf-Hirschhorn	WHSC1	44928	44928	44928	2	43897	1032	6635	>100	2

	_at	.1	syndrome candidate 1										
63	222778 _s_at	AI770166	Wolf-Hirschhorn syndrome candidate 1	WHSC1	44928	44928	44928	3	42704	2225	7936	>100	3
64	209054 _s_at	AF083389 .1	Wolf-Hirschhorn syndrome candidate 1	WHSC1	44928	44928	44928	4	44524	405	444	>100	4
65	222777 _s_at	AI770166	Wolf-Hirschhorn syndrome candidate 1	WHSC1	44928	44928	44928	5	41834	3095	13244	>100	5
66	209053 _s_at	AF083389 .1	Wolf-Hirschhorn syndrome candidate 1	WHSC1	44928	44928	44928	7	42426	2503	10341	>100	7
67	200921 _s_at	NM_0017 31.1	B-cell translocation gene 1, anti-proliferative	BTG1	75	44928	27	44928	260	44669	787	24	24
68	209052 _s_at	AF083389 .1	Wolf-Hirschhorn syndrome candidate 1	WHSC1	44928	44928	44928	24	42989	1940	4673	>100	24
69	213940 _s_at	AU14505 3	formin binding protein 1	FNBP1	44928	44928	43	44928	7005	37924	11991	>100	43
70	213732 _at	BE962186	transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47)	TCF3	44928	44928	44928	44928	44876	53	200	>100	53
71	213047 _x_at	AI278616	SET translocation (myeloid leukemia-associated)	SET	44928	44928	74	44928	85	44844	207	>100	74
72	200631 _s_at	NM_0030 11.1	SET translocation (myeloid leukemia-associated)	SET	130	44928	44928	44928	175	44754	642	81	81
73	205068 _s_at	BE671084	GTPase regulator associated with focal adhesion kinase pp125(FAK)	GRAF	44928	44928	44928	44928	44830	99	190	>100	99
74	220146 _at	NM_0165 62.1	toll-like receptor 7	TLR7	10	44928	44928	44928	961	43968	9515	>100	10
75	232304 _at	AK02671 4.1	pellino homolog 1 (Drosophila)	PELI1	44928	44928	44928	13	44623	306	766	>100	13
76	232213	AU14750	pellino homolog 1	PELI1	44928	44928	44928	18	44653	276	1025	>100	18

	_at	6	(Drosophila)										
77	218319 _at	NM_0206 51.2	pellino homolog 1 (Drosophila)	PELI1	44928	44928	44928	38	41381	3548	3985	>100	38
78	215744 _at	AW51414 0	fusion, derived from t(12;16) malignant liposarcoma	FUS	44928	44928	44928	44928	44853	76	158	>100	76
79	206363 _at	NM_0053 60.2	v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian)	MAF	44928	44928	44928	8	34192	10737	7331	>100	8
80	202768 _at	NM_0067 32.1	FBJ murine osteosarcoma viral oncogene homolog B	FOSB	44928	44928	44928	51	43123	1806	2597	>100	51
81	202647 _s_at	NM_0025 24.2	neuroblastoma RAS viral (v-ras) oncogene homolog	NRAS	78	44928	52	44928	169	44760	691	>100	52
82	209640 _at	M79462.1	promyelocytic leukemia	PML	44928	44928	44928	44928	44851	78	115	>100	78
140	232231 _at	AL353944 .1	Runt domain transcription factor 2	RUNX2	1	44928	1	44928	17	44912	212	1	1
83	201575 _at	NM_0122 45.1	SKI-interacting protein	SNW1	44928	44928	44928	44928	3	44926	12	>100	3
84	224985 _at	BE964484	Homo sapiens, clone IMAGE:3446533, mRNA	---	31	44928	13	44928	54	44875	130	6	6
85	204602 _at	NM_0122 42.1	dickkopf homolog 1 (Xenopus laevis)	DKK1	44928	44928	10	44928	2757	42172	9868	>100	10
86	201653 _at	NM_0057 76.1	cornichon homolog (Drosophila)	CNIH	44928	44928	45	44928	16	44913	26	94	16
87	234021 _at	AK02498 4.1	Homo sapiens cDNA: FLJ21331 fis, clone COL02520.	---	44928	44928	44928	44928	44909	20	16	>100	16
88	212063 _at	BE903880	CD44 antigen (homing function and Indian	CD44	44928	44928	18	44928	2720	42209	8726	62	18

			blood group system)										
89	204489_s_at	NM_000610.1	CD44 antigen (homing function and Indian blood group system)	CD44	34	44928	54	44928	3784	41145	21033	>100	34
90	227167_s_at	AW511319	Homo sapiens mesenchymal stem cell protein DSC96 mRNA, partial cds	---	44928	44928	37	44928	155	44774	430	>100	37
91	202290_at	NM_014891.1	PDGFA associated protein 1	PDAP1	44928	44928	44928	44928	78	44851	108	>100	78
92	215499_at	AA780381	mitogen-activated protein kinase kinase 3	MAP2K3	44928	44928	44928	78	44259	670	1433	>100	78
93	200047_s_at	NM_003403.2	YY1 transcription factor	YY1	44928	44928	44928	44928	135	44794	193	95	95
94	222555_s_at	AI338045	mitochondrial ribosomal protein L44	MRPL44	44928	44928	44928	44928	4	44925	11	>100	4
95	212694_s_at	NM_000532.1	propionyl Coenzyme A carboxylase, beta polypeptide	PCCB	44928	44928	44928	44928	7	44922	19	>100	7
96	222530_s_at	AF275813.1	McKusick-Kaufman syndrome	MKKS	69	44928	129	44928	13	44916	15	42	13
97	200869_at	NM_000980.1	ribosomal protein L18a	RPL18A	20	44928	97	44928	723	44206	2697	76	20
98	200023_s_at	NM_003754.1	eukaryotic translation initiation factor 3, subunit 5 epsilon, 47kDa	EIF3S5	29	44928	65	44928	178	44751	992	21	21
99	200812_at	NM_006429.1	chaperonin containing TCP1, subunit 7 (eta)	CCT7	44928	44928	44928	44928	22	44907	25	>100	22
100	225190_x_at	AW402660	ribosomal protein L35a	RPL35A	27	44928	44928	44928	423	44506	1445	27	27
101	200023_s_at	NM_003754.1	eukaryotic translation initiation factor 3, subunit 5 epsilon, 47kDa	EIF3S5	58	44928	51	44928	182	44747	332	31	31
102	217919	BE782148	mitochondrial ribosomal	MRPL42	44928	44928	82	44928	60	44869	34	>100	34

	_s_at		protein L42										
103	211972 _x_at	AI953822	ribosomal protein, large, P0	RPLP0	92	44928	44928	44928	378	44551	420	38	38
104	200024 _at	NM_001009.1	ribosomal protein S5	RPS5	118	44928	93	44928	122	44807	333	41	41
105	200715 _x_at	BC000514.1	ribosomal protein L13a	RPL13A	47	44928	114	44928	2857	42072	9548	>100	47
106	201258 _at	NM_001020.1	ribosomal protein S16	RPS16	99	44928	99	44928	185	44744	738	51	51
107	200003 _s_at	NM_000991.1	ribosomal protein L28	RPL28	56	44928	44928	44928	2488	42441	9320	>100	56
108	221726 _at	BE250348	ribosomal protein L22	RPL22	44928	44928	115	44928	206	44723	657	64	64
109	200041 _s_at	NM_004640.1	HLA-B associated transcript 1	BAT1	44928	44928	44928	70	33237	11692	18501	>100	70
110	211937 _at	NM_001417.1	eukaryotic translation initiation factor 4B	EIF4B	44928	44928	71	44928	794	44135	2480	>100	71
111	200082 _s_at	AI805587	ribosomal protein S7	RPS7	72	44928	84	44928	468	44461	1272	85	72
112	214167 _s_at	AA555113	ribosomal protein, large, P0	RPLP0	44928	44928	107	44928	239	44690	326	73	73
113	200024 _at	NM_001009.1	ribosomal protein S5	RPS5	152	44928	44928	44928	156	44773	546	77	77
114	217719 _at	NM_016091.1	eukaryotic translation initiation factor 3, subunit 6 interacting protein	EIF3S6IP	44928	44928	44928	44928	532	44397	951	78	78
115	225797 _at	AV707568	mitochondrial ribosomal protein L54	MRPL54	166	44928	138	44928	108	44821	312	83	83
116	200937 _s_at	NM_000969.1	ribosomal protein L5	RPL5	44928	44928	89	44928	1188	43741	3462	>100	89
117	208985 _s_at	BC002719.1	eukaryotic translation initiation factor 3, subunit 1 alpha, 35kDa	EIF3S1	105	44928	44928	44928	90	44839	199	>100	90

118	200834_s_at	NM_001024.1	ribosomal protein S21	RPS21	109	44928	136	44928	870	44059	4275	98	98
119	216153_x_at	AK022897.1	reversion-inducing-cysteine-rich protein with kazal motifs	RECK	44928	3	44928	9	44724	205	1125	>100	3
120	217687_at	AA224446	adenylate cyclase 2 (brain)	ADCY2	44928	44928	44928	44928	44923	6	28	>100	6
121	222632_s_at	AA843132	leucine zipper transcription factor-like 1	LZTFL1	44928	44928	22	44928	559	44370	962	>100	22
122	236623_at	AI367432	hypothetical protein MGC16179	MGC16179	44928	33	44928	44928	43090	1839	11437	>100	33
123	221899_at	AI809961	hypothetical protein from BCRA2 region	CG005	44928	41	44928	44928	40910	4019	11859	>100	41
124	221691_x_at	AB042278.1	nucleophosmin (nucleolar phosphoprotein B23, numatrin)	NPM1	43	44928	44928	44928	926	44003	3231	>100	43
125	209030_s_at	NM_014333.1	immunoglobulin superfamily, member 4	IGSF4	44928	44928	44	44928	2842	42087	9276	>100	44
126	222762_x_at	AU144259	LIM domains containing 1	LIMD1	44928	44928	57	44928	1570	43359	4714	>100	57
127	240983_s_at	AW292273	cysteinyl-tRNA synthetase	CARS	44928	44928	80	44928	1536	43393	2413	>100	80
128	200713_s_at	NM_012325.1	microtubule-associated protein, RP/EB family, member 1	MAPRE1	44928	44928	44928	44928	96	44833	300	>100	96
129	200814_at	NM_006263.1	proteasome (prosome, macropain) activator subunit 1 (PA28 alpha)	PSME1	44928	44928	130	44928	14	44915	31	44	14
130	201532_at	NM_002788.1	proteasome (prosome, macropain) subunit, alpha type, 3	PSMA3	76	44928	30	44928	19	44910	22	26	19
131	218011	NM_0242	ubiquitin-like 5	UBL5	44928	44928	94	44928	39	44890	90	47	39

	_at	92.1											
132	224747_at	AK000617.1	hypothetical protein LOC92912	LOC92912	44928	44928	44928	44928	391	44538	706	45	45
133	201758_at	NM_006292.1	tumor susceptibility gene 101	TSG101	44928	44928	44928	44928	65	44864	171	>100	65
134	200019_s_at	NM_001997.1	Finkel-Biskis-Reilly murine sarcoma virus (FBR-MuSV) ubiquitously expressed (fox derived); ribosomal protein S30	FAU	156	44928	44928	44928	220	44709	640	68	68
135	202346_at	NM_005339.2	huntingtin interacting protein 2	HIP2	44928	44928	44928	44928	79	44850	255	>100	79
136	201177_s_at	NM_005499.1	SUMO-1 activating enzyme subunit 2	UBA2	44928	44928	143	44928	81	44848	170	87	81
137	200043_at	NM_004450.1	enhancer of rudimentary homolog (Drosophila)	ERH	44928	44928	140	44928	1	44928	7	22	1
138	212109_at	AK023154.1	HN1 like	HN1L	44928	44928	44928	44928	44928	1	4	>100	1
139	212190_at	AL541302	serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 2	SERPINE2	44928	44928	44928	1	44650	279	325	>100	1
141	234428_at	AL110127.1	Homo sapiens mRNA; cDNA DKFZp564I1316 (from clone DKFZp564I1316)	---	44928	44928	44928	44928	44927	2	1	>100	1
142	235102_x_at	AI684439	phenylalanine hydroxylase	PAH	44928	1	44928	6	44469	460	4356	>100	1
143	200965_s_at	NM_006720.1	actin binding LIM protein 1	ABLIM1	44928	44928	44928	44928	44919	10	2	>100	2
144	222783	NM_022117	SPARC related modular	SMOC1	22	44928	3	44928	72	44857	117	2	2

	_s_at	37.1	calcium binding 1										
145	232075 _at	BF791874	recombination protein REC14	REC14	5	44928	31	44928	2	44927	8	3	2
146	220565 _at	NM_016602.1	G protein-coupled receptor 2	GPR2	3	44928	14	44928	304	44625	851	5	3
147	220572 _at	NM_018705.1	hypothetical protein DKFZp547G183	DKFZp547G183	44928	44928	44928	44928	44926	3	3	>100	3
148	208263 _at	NM_018581.1	---	---	44928	44928	44928	44928	44903	26	5	>100	5
149	221569 _at	AL136797.1	hypothetical protein FLJ20069	FLJ20069	44928	9	44928	48	44924	5	13	>100	5
150	222427 _s_at	AK021413.1	leucyl-tRNA synthetase	LARS	12	44928	76	44928	5	44924	36	9	5
151	230941 _at	AI651340	Homo sapiens, clone IMAGE:5271446, mRNA	---	44928	5	44928	44928	44738	191	96	>100	5
152	201682 _at	NM_004279.1	peptidase (mitochondrial processing) beta	PMPCB	38	44928	73	44928	6	44923	10	20	6
153	210258 _at	AF030107.1	regulator of G-protein signalling 13	RGS13	44928	44928	6	44928	3847	41082	26318	>100	6
154	218438 _s_at	NM_025205.1	endothelial-derived gene 1	EG1	60	44928	44928	44928	10	44919	6	>100	6
155	227341 _at	AW195407	Homo sapiens mRNA; cDNA DKFZp686C072 (from clone DKFZp686C072)	---	44928	6	44928	44928	43167	1762	10075	>100	6
156	202075 _s_at	NM_006227.1	phospholipid transfer protein	PLTP	44928	7	44928	44928	39569	5360	20579	>100	7
157	216288 _at	AU159276	cysteinyl leukotriene receptor 1	CYSLTR1	44928	44928	44928	44928	44922	7	46	>100	7
158	217915 _s_at	NM_016304.1	chromosome 15 open reading frame 15	C15orf15	33	44928	35	44928	11	44918	14	7	7
159	222968 _at	NM_016947.1	chromosome 6 open reading frame 48	C6orf48	7	44928	11	44928	107	44822	481	43	7

160	202567_at	NM_004175.1	small nuclear ribonucleoprotein D3 polypeptide 18kDa	SNRPD3	44928	44928	28	44928	8	44921	32	28	8
161	213510_x_at	AW194543	TL132 protein	LOC220594	44928	8	44928	34	44098	831	2375	>100	8
162	225065_x_at	AI826279	hypothetical protein MGC40157	MGC40157	41	44928	33	44928	68	44861	92	8	8
163	204287_at	NM_004711.1	synaptogyrin 1	SYNGR1	44928	44928	44928	44928	44920	9	24	>100	9
164	206762_at	NM_002234.1	potassium voltage-gated channel, shaker-related subfamily, member 5	KCNA5	9	44928	44928	44928	1038	43891	20489	>100	9
165	210250_x_at	AF067854.1	adenylosuccinate lyase	ADSL	44928	44928	44928	44928	9	44920	27	>100	9
166	210497_x_at	BC002818.1	synovial sarcoma, X breakpoint 2	SSX2	44928	44928	9	44928	651	44278	3927	>100	9
167	223358_s_at	AW269834	Homo sapiens cDNA FLJ33024 fis, clone THYMU1000532, moderately similar to HIGH-AFFINITY CAMP-SPECIFIC 3',5'-CYCLIC PHOSPHODIESTERASE (EC 3.1.4.17).	---	54	44928	39	44928	99	44830	366	10	10
168	225767_at	AL531684	ESTs, Weakly similar to T02345 hypothetical protein KIAA0324 - human (fragment) [H.sapiens]	---	44928	10	44928	44928	31271	13658	34008	>100	10
169	232169_x_at	AK002110.1	NADH dehydrogenase (ubiquinone) Fe-S protein 8, 23kDa (NADH-coenzyme Q	NDUFS8	44928	44928	44928	10	44849	80	245	>100	10

			reductase)										
170	216287_at	AK021930.1	---	---	44928	44928	44928	44928	44918	11	52	>100	11
171	228332_s_at	AA526939	selenoprotein H	SELH	55	44928	149	44928	38	44891	67	11	11
172	242903_at	AI458949	ESTs	---	44928	44928	44928	11	44599	330	1363	>100	11
173	244114_x_at	AI003508	ESTs	---	11	44928	44928	44928	3539	41390	33890	>100	11
174	223490_s_at	AF281132.1	exosome component Rrp40	RRP40	44928	44928	44928	44928	12	44917	29	>100	12
175	224496_s_at	BC006292.1	hypothetical protein MGC10744	MGC10744	44928	12	44928	44	40920	4009	11871	>100	12
176	226243_at	BF590958	hypothetical protein MGC11266	MGC11266	44928	44928	12	44928	97	44832	49	49	12
177	231045_x_at	H29876	selenoprotein H	SELH	44928	44928	121	44928	28	44901	39	12	12
178	206978_at	NM_000647.2	chemokine (C-C motif) receptor 2	CCR2	82	44928	20	44928	818	44111	2153	13	13
179	212062_at	AB014511.1	ATPase, Class II, type 9A	ATP9A	44928	13	44928	44928	44776	153	45	>100	13
180	227692_at	AU153866	guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 1	GNAI1	44928	44928	44928	44928	44916	13	21	>100	13
181	200710_at	NM_000018.1	acyl-Coenzyme A dehydrogenase, very long chain	ACADVL	44928	14	44928	69	44212	717	2804	>100	14
182	216529_at	AL049244.1	Homo sapiens mRNA; cDNA DKFZp564C163 (from clone DKFZp564C163)	---	44928	44928	44928	44928	44915	14	75	>100	14
183	233437_at	AF238869.1	gamma-aminobutyric acid (GABA) A	GABRA4	44928	36	44928	14	44817	112	455	>100	14

			receptor, alpha 4										
184	202591_s_at	NM_003143.1	single-stranded DNA binding protein	SSBP1	44928	44928	44928	44928	15	44914	69	75	15
185	206632_s_at	NM_004900.1	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B	APOBEC3B	61	44928	15	44928	386	44543	1554	65	15
186	213975_s_at	AV711904	lysozyme (renal amyloidosis)	LYZ	44928	44928	44928	15	39536	5393	16729	>100	15
187	224493_x_at	BC006280.1	hypothetical protein MGC11386	MGC11386	44928	15	44928	44928	44792	137	450	>100	15
188	226392_at	AI888503	Homo sapiens cDNA: FLJ21652 fis, clone COL08582.	---	112	44928	69	44928	80	44849	94	15	15
189	235666_at	AA903473	ESTs, Weakly similar to hypothetical protein FLJ20489 [Homo sapiens] [H.sapiens]	---	15	44928	44928	44928	2414	42515	6329	58	15
190	205807_s_at	NM_020127.1	tuftelin 1	TUFT1	44928	44928	44928	44928	44913	16	44	>100	16
191	206121_at	NM_000036.1	adenosine monophosphate deaminase 1 (isoform M)	AMPD1	44928	44928	16	44928	236	44693	516	23	16
192	207697_x_at	NM_005874.1	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 2	LILRB2	44928	16	44928	44928	43348	1581	11408	>100	16
193	207912_s_at	NM_004081.2	deleted in azoospermia	DAZ	16	44928	44928	44928	1052	43877	10620	>100	16
194	222315_at	AW972855	ESTs	---	44928	44928	44928	16	40968	3961	5887	>100	16
195	58367_s_at	AA429615	hypothetical protein FLJ23233	FLJ23233	44928	44928	44928	44928	44912	17	53	>100	17

196	214657_s_at	AU134977	Human clone 137308 mRNA, partial cds.	---	44928	17	44928	21	44515	414	1432	>100	17
197	217466_x_at	L48784	---	---	44928	44928	17	44928	527	44402	1267	18	17
198	220232_at	NM_024906.1	hypothetical protein FLJ21032	FLJ21032	44928	44928	44928	17	44432	497	1066	>100	17
199	225698_at	BF314746	TIGA1	TIGA1	53	44928	46	44928	342	44587	1351	17	17
200	232010_at	AA129444	hypothetical protein DKFZp566D234	DKFZp566D234	17	44928	44928	44928	614	44315	6850	86	17
201	219429_at	NM_024306.1	fatty acid hydroxylase	FAAH	44928	44928	44928	44928	44863	66	18	>100	18
202	225981_at	AW139549	chromosome 17 open reading frame 28	C17orf28	44928	44928	44928	44928	44911	18	83	>100	18
203	229483_at	AA760738	ESTs	---	44928	18	44928	44928	44712	217	612	>100	18
204	235940_at	AW983691	hypothetical protein MGC10999	MGC10999	71	44928	66	44928	18	44911	40	84	18
205	204836_at	NM_000170.1	glycine dehydrogenase (decarboxylating; glycine decarboxylase, glycine cleavage system protein P)	GLDC	19	44928	44928	44928	2228	42701	23086	99	19
206	210800_at	BC005236.1	hypothetical protein MGC12262	MGC12262	44928	44928	44928	44928	44910	19	62	>100	19
207	222465_at	AF165521.1	chromosome 15 open reading frame 15	C15orf15	44928	44928	83	44928	46	44883	82	19	19
208	222784_at	NM_022137.1	SPARC related modular calcium binding 1	SMOC1	44928	44928	19	44928	1100	43829	4324	>100	19
209	225710_at	H99792	Homo sapiens cDNA FLJ34013 fis, clone FCBBF2002111.	---	44928	44928	44928	19	44375	554	688	>100	19
210	229170_s_at	AW024437	tetratricopeptide repeat-containing protein	LOC118491	44928	19	44928	92	43950	979	5702	>100	19

211	219373_at	NM_018973.1	dolichyl-phosphate mannosyltransferase polypeptide 3	DPM3	44928	20	44928	44928	38207	6722	15777	>100	20
212	221532_s_at	AF309553.1	recombination protein REC14	REC14	44928	44928	132	44928	25	44904	20	88	20
213	226882_x_at	AI861913	WD repeat domain 4	WDR4	44928	44928	26	44928	20	44909	38	>100	20
214	222410_s_at	AF121856.1	sorting nexin 6	SNX6	173	44928	50	44928	21	44908	35	39	21
215	225177_at	AA143793	Rab coupling protein	RCP	44928	21	44928	44928	43188	1741	4334	>100	21
216	243178_at	AW969703	ESTs, Weakly similar to hypothetical protein FLJ20489 [Homo sapiens] [H.sapiens]	---	44928	44928	44928	44928	44908	21	50	>100	21
217	205671_s_at	NM_002120.1	major histocompatibility complex, class II, DO beta	HLA-DOB	44928	25	44928	22	44677	252	596	>100	22
218	232538_at	AK027226.1	Homo sapiens cDNA: FLJ23573 fis, clone LNG12520.	---	44928	22	44928	29	44459	470	2019	>100	22
219	208151_x_at	NM_030881.1	DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 17, 72kDa	DDX17	44928	44928	44928	23	42362	2567	8455	>100	23
220	214246_x_at	AI859060	misshapen/NIK-related kinase	MINK	44928	23	44928	93	44744	185	1197	>100	23
221	223996_s_at	AF151083.1	mitochondrial ribosomal protein L30	MRPL30	44928	44928	44928	44928	23	44906	37	>100	23
222	224330_s_at	AB049647.1	mitochondrial ribosomal protein L27	MRPL27	44928	44928	59	44928	31	44898	23	>100	23
223	227174_at	Z98443	ESTs	---	23	44928	44928	44928	1433	43496	8774	>100	23
224	235875_at	BF510711	ESTs	---	44928	44928	44928	44928	44906	23	65	>100	23

225	201520_s_at	NM_002092.1	G-rich RNA sequence binding factor 1	GRSF1	44928	44928	102	44928	24	44905	61	>100	24
226	211276_at	AF063606.1	my048 protein	my048	44928	24	44928	44928	44693	236	186	>100	24
227	223395_at	AB056106.1	DKFZP586L2024 protein	NESHBP	24	44928	44928	44928	4177	40752	26522	>100	24
228	237429_at	AI677858	ESTs	---	44928	44928	44928	44928	44905	24	99	>100	24
229	215604_x_at	AK023783.1	---	---	44928	44928	44928	44928	44904	25	148	>100	25
230	239092_at	BF939224	ESTs, Highly similar to ITA8_HUMAN Integrin alpha-8 [H.sapiens]	---	25	44928	44928	44928	151	44778	1162	>100	25
231	211747_s_at	BC005938.1	LSM5 homolog, U6 small nuclear RNA associated (S. cerevisiae)	LSM5	122	44928	44928	44928	26	44903	54	50	26
232	216274_s_at	N99438	signal peptidase complex (18kD)	SPC18	26	44928	44928	44928	102	44827	359	34	26
233	236427_at	BF830560	ESTs	---	44928	26	44928	44928	44074	855	2194	>100	26
234	203058_s_at	AW299958	3'-phosphoadenosine 5'-phosphosulfate synthase 2	PAPSS2	44928	27	44928	44928	44761	168	593	>100	27
235	200043_at	NM_004450.1	enhancer of rudimentary homolog (Drosophila)	ERH	44928	44928	47	44928	27	44902	63	40	27
236	234087_at	AK022343.1	EST, Moderately similar to hypothetical protein FLJ20294 [Homo sapiens] [H.sapiens]	---	44928	29	44928	44928	44902	27	79	>100	27
237	242311_x_at	H37943	ESTs, Weakly similar to hypothetical protein FLJ20489 [Homo sapiens] [H.sapiens]	---	44928	44928	44928	27	44590	339	667	>100	27

238	213307_at	AB028945.1	SH3 and multiple ankyrin repeat domains 2	SHANK2	44928	44928	44928	44928	44901	28	43	>100	28
239	237414_at	H70477	coagulation factor VII (serum prothrombin conversion accelerator)	F7	44928	44928	44928	28	44539	390	2002	>100	28
240	239555_at	W87626	ESTs	---	44928	28	44928	44928	40008	4921	12979	>100	28
241	222893_s_at	AI609064	hypothetical protein FLJ13150	FLJ13150	44928	44928	44928	44928	29	44900	47	>100	29
242	225647_s_at	AI246687	cathepsin C	CTSC	44928	44928	29	44928	56	44873	30	>100	29
243	233876_at	AK000677.1	Homo sapiens cDNA FLJ20670 fis, clone KAIA4743.	---	44928	44928	44928	44928	44900	29	105	>100	29
244	201554_x_at	NM_004130.1	glycogenin	GYG	128	44928	40	44928	67	44862	387	30	30
245	203561_at	NM_021642.1	Fc fragment of IgG, low affinity IIa, receptor for (CD32)	FCGR2A	44928	44928	44928	97	44899	30	74	>100	30
246	214594_x_at	BG252666	ATPase, Class I, type 8B, member 1	ATP8B1	44928	44928	44928	30	44816	113	236	>100	30
247	219030_at	NM_016058.1	CGI-121 protein	CGI-121	44928	44928	44928	44928	30	44899	56	>100	30
248	219233_s_at	NM_018530.1	hypothetical protein PRO2521	PRO2521	44928	30	44928	44928	44418	511	1342	>100	30
249	242135_at	AA927533	Homo sapiens cDNA FLJ32537 fis, clone SMINT2000400, highly similar to Homo sapiens FRG1 mRNA.	---	30	44928	44928	44928	661	44268	3000	>100	30
250	228726_at	AW512196	ESTs, Weakly similar to hypothetical protein FLJ20489 [Homo	---	44928	42	44928	44928	44898	31	84	>100	31

			sapiens] [H.sapiens]										
251	208642_s_at	AA205834	X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining; Ku autoantigen, 80kDa)	XRCC5	44928	44928	161	44928	32	44897	70	74	32
252	220725_x_at	NM_025095.1	hypothetical protein FLJ23558	FLJ23558	44928	32	44928	44928	44060	869	2613	>100	32
253	220755_s_at	NM_016947.1	chromosome 6 open reading frame 48	C6orf48	32	44928	64	44928	431	44498	1780	35	32
254	229269_x_at	BF976372	myo-inositol 1-phosphate synthase A1	ISYNA1	44928	44928	32	44928	809	44120	3681	>100	32
255	232659_at	AU146864	Homo sapiens cDNA FLJ12017 fis, clone HEMBB1001735.	---	44928	44928	44928	44928	44897	32	178	>100	32
256	244042_x_at	AA883831	ESTs	---	44928	44928	44928	32	44833	96	120	>100	32
257	204518_s_at	NM_000943.1	peptidylprolyl isomerase C (cyclophilin C)	PPIC	44928	44928	44928	33	44763	166	841	>100	33
258	205500_at	NM_001735.1	complement component 5	C5	44928	44928	44928	44928	44896	33	86	>100	33
259	209345_s_at	AL561930	phosphatidylinositol 4-kinase type II	PI4KII	44928	44928	44928	44928	44890	39	33	>100	33
260	222531_s_at	AW137526	chromosome 14 open reading frame 108	C14orf108	44928	44928	41	44928	33	44896	111	54	33
261	224709_s_at	AF131831.1	non-kinase Cdc42 effector protein SPEC2	SPEC2	143	44928	62	44928	280	44649	857	33	33
262	209427_at	AF064238.3	smoothelin	SMTN	44928	44928	44928	44928	44895	34	59	>100	34
263	236254_at	BE048857	hypothetical protein MGC45726	MGC45726	44928	34	44928	44928	44254	675	2739	>100	34
264	201056	N53479	Homo sapiens cDNA	---	44928	44928	44928	44928	44894	35	66	>100	35

	_at		FLJ37232 fis, clone BRAMY2001114.										
265	205644_s_at	NM_003096.1	small nuclear ribonucleoprotein polypeptide G	SNRPG	155	44928	44928	44928	35	44894	77	37	35
266	228919_at	AA601031	ESTs, Highly similar to cell division cycle 2-like 1, isoform 1; Cell division cycle 2-like 1; PITSLRE protein kinase alpha; p58/GTA protein kinase; galactosyltransferase associated protein kinase; CDC-related protein kinase p58; PITSLRE B [Homo sapiens] [H.sapiens]	---	44928	44928	44928	35	41176	3753	12711	>100	35
267	231131_at	AA909330	hypothetical protein FLJ37659	FLJ37659	35	44928	44928	44928	1469	43460	6555	71	35
268	240587_x_at	AI478814	ESTs	---	44928	35	44928	44928	36474	8455	27078	>100	35
269	AFFX-HUMRGE/M10098_M_at	M10098	---	---	44928	44928	44928	36	25931	18998	37580	>100	36
270	212238_at	AL117518.1	additional sex combs like 1 (Drosophila)	ASXL1	44928	44928	44928	44928	44893	36	80	>100	36
271	221434_s_at	NM_031210.1	hypothetical protein DC50	DC50	44928	44928	44928	44928	36	44893	103	>100	36
272	223029_s_at	AL136921.1	ring finger and WD repeat domain 1	RFWD1	39	44928	36	44928	104	44825	1374	>100	36
273	227641	AI613010	hypothetical protein	MGC339	36	44928	105	44928	124	44805	313	>100	36

	_at		MGC33974	74									
274	206323_x_at	NM_002547.1	oligophrenin 1	OPHN1	44928	44928	44928	37	44545	384	324	>100	37
275	211424_x_at	AF113007.1	DKFZP586A0522 protein	DKFZP586A0522	44928	37	44928	77	44775	154	575	>100	37
276	215322_at	AL080190.1	Homo sapiens mRNA; cDNA DKFZp434A202 (from clone DKFZp434A202)	---	44928	44928	44928	44928	44892	37	116	>100	37
277	222713_s_at	AF181995.1	Fanconi anemia, complementation group F	FANCF	160	44928	154	44928	37	44892	151	>100	37
278	228496_s_at	AW243081	cysteine-rich motor neuron 1	CRIM1	37	44928	44928	44928	5459	39470	29457	>100	37
279	221223_x_at	NM_013324.2	cytokine inducible SH2-containing protein	CISH	44928	44928	44928	44928	44891	38	57	>100	38
280	224673_at	AI613244	---	---	44928	38	44928	67	44728	201	561	>100	38
281	224841_x_at	BF316352	Homo sapiens mRNA; cDNA DKFZp564D0164 (from clone DKFZp564D0164)	---	104	44928	38	44928	1040	43889	3386	46	38
282	237266_at	BE552347	Kv channel interacting protein 2	KCNIP2	44928	39	44928	44928	43140	1789	11320	>100	39
283	244357_at	T90760	ESTs	---	44928	44928	44928	39	43992	937	3272	>100	39
284	228434_at	AA806965	Homo sapiens, Similar to hypothetical protein B430208I01, clone IMAGE:5181522, mRNA, partial cds	---	44928	44928	44928	40	44467	462	1357	>100	40
285	232746_at	BE552368	Homo sapiens cDNA FLJ13445 fis, clone	---	44928	44928	44928	44928	44889	40	64	>100	40

			PLACE1002962.										
286	37793_r_at	AF034956	RAD51-like 3 (S. cerevisiae)	RAD51L3	44928	44928	44928	44928	44888	41	126	>100	41
287	203408_s_at	NM_002971.1	special AT-rich sequence binding protein 1 (binds to nuclear matrix/scaffold-associating DNA's)	SATB1	44928	44928	44928	41	43257	1672	1941	>100	41
288	207124_s_at	NM_006578.1	guanine nucleotide binding protein (G protein), beta 5	GNB5	44928	44928	44928	44928	41	44888	184	>100	41
289	208844_at	BC002456.1	---	---	44928	44928	44928	44928	44887	42	137	>100	42
290	218139_s_at	NM_018229.1	chromosome 14 open reading frame 108	C14orf108	44928	44928	44928	44928	42	44887	55	>100	42
291	224579_at	AK024263.1	Homo sapiens cDNA FLJ14201 fis, clone NT2RP3002955.	---	44928	44928	42	44928	400	44529	757	52	42
292	244359_s_at	H28915	ESTs	---	42	44928	44928	44928	3802	41127	28000	>100	42
293	53987_at	AL041852	KIAA1464 protein	KIAA1464	44928	44928	44928	44928	44886	43	127	>100	43
294	212307_s_at	BF001665	O-linked N-acetylglucosamine (GlcNAc) transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylglucosaminyl transferase)	OGT	44928	43	44928	44928	33355	11574	18158	>100	43
295	232098_at	AK025142.1	ESTs	---	44928	44928	44928	43	42790	2139	2890	>100	43
296	215908_at	AF009267.1	Homo sapiens full length insert cDNA	---	44928	44	44928	44928	44462	467	1470	>100	44

			YU79F10										
297	217294_s_at	U88968.1	enolase 1, (alpha)	ENO1	44	44928	44928	44928	47	44882	135	>100	44
298	220852_at	NM_014099.1	PRO1768 protein	PRO1768	44928	44928	44928	44928	44885	44	102	>100	44
299	225402_at	BG339450	chromosome 20 open reading frame 64	C20orf64	44928	44928	44928	44928	44	44885	78	>100	44
300	212923_s_at	AK024828.1	hypothetical protein LOC221749	LOC221749	44928	44928	44928	44928	44884	45	123	>100	45
301	222714_s_at	BC000878.1	CGI-83 protein	CGI-83	44928	44928	44928	44928	45	44884	104	>100	45
302	229050_s_at	AL533103	Homo sapiens cDNA FLJ30346 fis, clone BRACE2007527.	---	45	44928	44928	44928	2495	42434	6112	>100	45
303	240593_x_at	R98767	ESTs, Weakly similar to hypothetical protein FLJ20378 [Homo sapiens] [H.sapiens]	---	44928	45	44928	44928	39771	5158	14507	>100	45
304	241722_x_at	BF724558	ESTs, Moderately similar to T02670 probable thromboxane A2 receptor isoform beta - human [H.sapiens]	---	44928	44928	44928	45	43069	1860	3871	>100	45
305	212110_at	D31887.1	KIAA0062 protein	KIAA0062	44928	46	44928	44928	27676	17253	28338	>100	46
306	215628_x_at	AL049285.1	Homo sapiens mRNA; cDNA DKFZp564M193 (from clone DKFZp564M193)	---	44928	44928	44928	46	44499	430	654	>100	46
307	236946_at	AI220134	ESTs	---	44928	44928	44928	44928	44883	46	204	>100	46
308	210992_x_at	U90939.1	Fc fragment of IgG, low affinity IIa, receptor for (CD32)	FCGR2A	44928	44928	44928	47	43239	1690	3640	>100	47

309	217527_s_at	AI478300	Homo sapiens, clone IMAGE:3659798, mRNA	---	44928	47	44928	44928	40926	4003	14691	>100	47
310	219183_s_at	NM_013385.2	pleckstrin homology, Sec7 and coiled/coil domains 4	PSCD4	44928	44928	44928	44928	44882	47	101	>100	47
311	200826_at	NM_004597.3	small nuclear ribonucleoprotein D2 polypeptide 16.5kDa	SNRPD2	165	44928	44928	44928	48	44881	221	89	48
312	203663_s_at	NM_004255.1	cytochrome c oxidase subunit Va	COX5A	44928	44928	110	44928	52	44877	48	>100	48
313	209049_s_at	BC001004.1	protein kinase C binding protein 1	PRKCBP1	44928	48	44928	44928	39921	5008	15023	>100	48
314	209486_at	BC004546.1	disrupter of silencing 10	SAS10	79	44928	48	44928	144	44785	600	57	48
315	213345_at	AI624015	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 4	NFATC4	44928	44928	44928	44928	44881	48	51	>100	48
316	223076_s_at	BC001041.1	hypothetical protein FLJ20303	FLJ20303	48	44928	44928	44928	566	44363	2838	69	48
317	224364_s_at	AF251049.1	peptidylprolyl isomerase (cyclophilin)-like 3	PPIL3	139	44928	44928	44928	121	44808	368	48	48
318	212750_at	AB020630.1	protein phosphatase 1, regulatory (inhibitor) subunit 16B	PPP1R16B	44928	44928	49	44928	953	43976	2373	>100	49
319	219203_at	NM_016049.1	CGI-112 protein	CGI-112	44928	44928	44928	44928	49	44880	271	>100	49
320	224741_x_at	BG329175	Homo sapiens mRNA; cDNA DKFZp564D0164 (from clone DKFZp564D0164)	---	49	44928	70	44928	1470	43459	5688	53	49
321	227062	AU15536	plectin 1, intermediate	PLEC1	44928	44928	44928	49	44613	316	708	>100	49

	_at	1	filament binding protein 500kDa										
322	232516_x_at	AU150385	YY1 associated protein	YAP	44928	44928	44928	101	44880	49	153	>100	49
323	207573_x_at	NM_006476.1	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit g	ATP5L	50	44928	44928	44928	168	44761	305	56	50
324	212644_s_at	AI671747	chromosome 14 open reading frame 32	C14orf32	44928	44928	44928	44928	50	44879	89	>100	50
325	231825_x_at	AK025060.1	activating transcription factor 7 interacting protein	ATF7IP	44928	44928	44928	44928	44879	50	152	>100	50
326	239331_at	AW954199	ESTs	---	44928	44928	44928	50	42943	1986	4181	>100	50
327	209733_at	AL034399	hypothetical protein LOC286440	LOC286440	44928	44928	44928	44928	44878	51	283	>100	51
328	230876_at	AI827906	hypothetical protein LOC169834	LOC169834	51	44928	44928	44928	658	44271	3954	>100	51
329	216750_at	AK024871.1	amyloid beta (A4) precursor protein-binding, family B, member 2 (Fe65-like)	APBB2	44928	44928	44928	44928	44877	52	277	>100	52
330	228728_at	BF724137	hypothetical protein FLJ21986	FLJ21986	52	44928	85	44928	215	44714	1139	>100	52
331	230014_at	BF515592	ESTs	---	44928	44928	44928	52	41139	3790	8523	>100	52
332	210715_s_at	AF027205.1	serine protease inhibitor, Kunitz type, 2	SPINT2	44928	44928	44928	53	40070	4859	8720	>100	53
333	218467_at	NM_020232.1	hepatocellular carcinoma susceptibility protein	HCCA3	44928	44928	44928	44928	53	44876	149	100	53
334	AFFX-HUMI	M97935	---	---	44928	44928	53	44928	708	44221	1068	>100	53

	SGF3A /M979 35_M A_at												
335	204227 _s_at	NM_0046 14.1	thymidine kinase 2, mitochondrial	TK2	44928	44928	44928	44928	44875	54	114	>100	54
336	232138 _at	AW27691 4	Homo sapiens clone IMAGE:713177, mRNA sequence	---	44928	44928	44928	54	44534	395	1280	>100	54
337	204517 _at	BE962749	peptidylprolyl isomerase C (cyclophilin C)	PPIC	44928	44928	44928	55	44402	527	978	>100	55
338	211275 _s_at	AF087942 .1	glycogenin	GYG	131	44928	44928	44928	369	44560	1427	55	55
339	226888 _at	BG10486 0	casein kinase 1, gamma 1	CSNK1G 1	44928	44928	44928	44928	55	44874	58	>100	55
340	AFFX-HUMI SGF3A /M979 35_MB _at	M97935	---	---	44928	44928	56	44928	454	44475	523	>100	56
341	225373 _at	BE271644	PP2135 protein	PP2135	44928	44928	44928	56	44814	115	372	>100	56
342	205618 _at	NM_0009 50.1	proline-rich Gla (G-carboxyglutamic acid) polypeptide 1	PRRG1	44928	44928	44928	44928	44872	57	81	>100	57
343	200030 _s_at	NM_0026 35.1	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 3	SLC25A 3	44928	44928	44928	44928	57	44872	91	67	57
344	228400 _at	AW02514 1	ESTs	---	57	44928	44928	44928	223	44706	1047	>100	57
345	201491 _at	NM_0121 11.1	chromosome 14 open reading frame 3	C14orf3	44928	44928	44928	44928	58	44871	107	>100	58

346	209031_at	NM_014333.1	immunoglobulin superfamily, member 4	IGSF4	44928	44928	58	44928	2854	42075	8458	>100	58
347	222529_at	BG251467	mitochondrial solute carrier protein	MSCP	44928	44928	44928	58	27388	17541	33137	>100	58
348	244142_at	D60329	ESTs	---	44928	44928	44928	44928	44871	58	125	>100	58
349	226227_x_at	BF185165	Homo sapiens, clone IMAGE:5285034, mRNA	---	73	44928	44928	44928	675	44254	1792	59	59
350	226830_x_at	BG339245	Homo sapiens cDNA FLJ14030 fis, clone HEMBA1004086.	---	44928	44928	44928	44928	59	44870	166	>100	59
351	233234_at	AB037738.1	KIAA1317 protein	KIAA1317	44928	44928	44928	59	44197	732	15108	>100	59
352	243147_x_at	AW118707	ESTs, Weakly similar to YYY1_HUMAN Very very hypothetical protein RMSA-1 [H.sapiens]	---	44928	44928	44928	44928	44870	59	68	>100	59
353	221458_at	NM_000866.1	5-hydroxytryptamine (serotonin) receptor 1F	HTR1F	44928	44928	44928	44928	44869	60	106	>100	60
354	225084_at	BG170743	SEC10-like 1 (S. cerevisiae)	SEC10L1	44928	44928	122	44928	69	44860	141	60	60
355	227598_at	AI762857	hypothetical protein BC011406	LOC113763	44928	44928	44928	44928	76	44853	60	>100	60
356	235113_at	AA742244	peptidylprolyl isomerase (cyclophilin) like 5	PPIL5	44928	44928	60	44928	200	44729	456	>100	60
357	242749_at	AI022173	ESTs	---	44928	44928	44928	60	43605	1324	4746	>100	60
358	AFFX-HUMRGE/M10098_M_at	M10098	---	---	44928	44928	44928	61	24464	20465	33430	>100	61
359	225281	AL117573	DKFZP434F2021	DKFZP4	44928	44928	44928	44928	132	44797	194	61	61

	_at	.1	protein	34F2021									
360	234942 _s_at	AK02522 0.1	---	---	44928	44928	44928	44928	61	44868	248	>100	61
361	213873 _at	D29810.1	endothelial and smooth muscle cell-derived neuropilin-like protein	ESDN	44928	44928	44928	44928	44867	62	73	>100	62
362	216524 _x_at	AL049260 .1	Homo sapiens mRNA; cDNA DKFZp564E233 (from clone DKFZp564E233)	---	44928	44928	44928	62	44161	768	1958	>100	62
363	231265 _at	AI126453	cytochrome c oxidase subunit VIIb2	COX7B2	62	44928	44928	44928	2009	42920	21140	>100	62
364	201264 _at	NM_0072 63.1	coatomer protein complex, subunit epsilon	COPE	80	44928	96	44928	176	44753	739	63	63
365	222510 _s_at	AI809203	makorin, ring finger protein, 2	MKRN2	44928	44928	44928	44928	63	44866	110	>100	63
366	226179 _at	N63920	Homo sapiens, clone IMAGE:5294823, mRNA	---	44928	44928	44928	63	27539	17390	31921	>100	63
367	226835 _s_at	BG33052 0	Homo sapiens, clone IMAGE:5285034, mRNA	---	44928	44928	63	44928	1324	43605	4164	>100	63
368	228159 _at	N45312	Homo sapiens cDNA FLJ38039 fis, clone CTONG2013934.	---	44928	44928	44928	44928	44866	63	290	>100	63
369	202026 _at	NM_0030 02.1	succinate dehydrogenase complex, subunit D, integral membrane protein	SDHD	44928	44928	44928	44928	64	44865	189	>100	64
370	220534 _at	NM_0241 14.1	tripartite motif-containing 48	TRIM48	44928	44928	44928	44928	44865	64	124	>100	64
371	239294 _at	AA81026 5	ESTs	---	64	44928	44928	44928	867	44062	3303	82	64
372	224298	BC004528	phosphoglycerate	PHGDH	65	44928	44928	44928	1198	43731	15433	>100	65

	_s_at	.1	dehydrogenase like 1	L1									
373	224558_s_at	BG483939	PRO1073 protein	PRO1073	44928	44928	44928	65	40007	4922	10881	>100	65
374	244172_at	AA931562	ESTs, Weakly similar to hypothetical protein FLJ20489 [Homo sapiens] [H.sapiens]	---	44928	44928	44928	85	44864	65	143	>100	65
375	205370_x_at	NM_001918.1	dihydrolipoamide branched chain transacylase (E2 component of branched chain keto acid dehydrogenase complex; maple syrup urine disease)	DBT	44928	44928	44928	66	44434	495	1851	>100	66
376	222789_at	BE888593	hypothetical protein FLJ11220	FLJ11220	44928	44928	44928	44928	66	44863	76	>100	66
377	226558_at	BE856637	ESTs	---	66	44928	44928	44928	751	44178	2501	>100	66
378	215109_at	R02172	ESTs, Moderately similar to hypothetical protein FLJ20234 [Homo sapiens] [H.sapiens]	---	44928	44928	44928	44928	44862	67	203	>100	67
379	224740_at	BE613001	Homo sapiens, clone IMAGE:4620009, mRNA	---	44928	44928	67	44928	426	44503	263	70	67
380	226265_at	AW294894	hypothetical protein FLJ21924	FLJ21924	67	44928	44928	44928	145	44784	397	>100	67
381	217188_s_at	AC007182	chromosome 14 open reading frame 1	C14orf1	68	44928	44928	44928	245	44684	508	>100	68
382	229466_at	AU144187	hypothetical protein LOC256273	LOC256273	44928	44928	44928	44928	44861	68	139	>100	68
383	242619	H82831	ESTs	---	44928	44928	44928	68	44810	119	408	>100	68

	_x_at												
384	220073_s_at	NM_018173.1	hypothetical protein FLJ10665	FLJ10665	44928	44928	44928	44928	44860	69	361	>100	69
385	210092_at	AF067173.1	mago-nashi homolog, proliferation-associated (Drosophila)	MAGOH	44928	44928	44928	44928	70	44859	157	>100	70
386	213371_at	AI803302	LIM domain binding 3	LDB3	44928	44928	44928	44928	44859	70	132	>100	70
387	229655_at	N66656	hypothetical protein CLONE25003	CLONE25003	70	44928	44928	44928	4007	40922	24679	>100	70
388	228866_at	BF514864	Homo sapiens cDNA FLJ13825 fis, clone THYRO1000558.	---	44928	44928	44928	71	43995	934	494	>100	71
389	244795_at	AV693986	ESTs	---	44928	44928	44928	44928	44858	71	273	>100	71
390	204610_s_at	NM_006848.1	hepatitis delta antigen-interacting protein A	DIPA	44928	44928	72	44928	1914	43015	8164	>100	72
391	225218_at	AA205754	hypothetical protein FLJ32919	FLJ32919	44928	44928	44928	44928	44857	72	169	>100	72
392	225904_at	N64686	Homo sapiens cDNA FLJ25935 fis, clone JTH06710.	---	87	44928	78	44928	1309	43620	4215	72	72
393	206992_s_at	NM_015684.1	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit s (factor B)	ATP5S	44928	44928	44928	44928	73	44856	145	>100	73
394	226944_at	AW518728	serine protease HTRA3	HTRA3	44928	44928	44928	44928	44856	73	196	>100	73
395	227084_at	AW339310	dystrobrevin, alpha	DTNA	44928	44928	44928	73	44615	314	833	>100	73
396	209703_x_at	BC004492.1	DKFZP586A0522 protein	DKFZP586A0522	44928	44928	44928	74	42035	2894	1118	>100	74
397	210154	M55905.1	malic enzyme 2,	ME2	44928	44928	44928	44928	74	44855	98	>100	74

	_at		NAD(+)-dependent, mitochondrial										
398	226050 _at	AL576117	chromosome 13 open reading frame 11	C13orf11	74	44928	44928	44928	1168	43761	5900	>100	74
399	209340 _at	S73498.1	UDP-N-acteylglucosamine pyrophosphorylase 1	UAP1	124	44928	75	44928	2926	42003	12143	79	75
400	215504 _x_at	AF131777 .1	Homo sapiens clone 25061 mRNA sequence	---	44928	44928	44928	75	44199	730	1434	>100	75
401	219878 _s_at	NM_0159 95.1	Kruppel-like factor 13	KLF13	44928	44928	44928	44928	75	44854	175	>100	75
402	221978 _at	BE138825	major histocompatibility complex, class I, F	HLA-F	44928	44928	44928	44928	44854	75	176	>100	75
403	226051 _at	BF973568	selenoprotein SelM	SELM	44928	44928	44928	76	43355	1574	2394	>100	76
404	208690 _s_at	BC000915 .1	PDZ and LIM domain 1 (elfin)	PDLIM1	77	44928	124	44928	1120	43809	3441	>100	77
405	213738 _s_at	AI587323	ATP synthase, H+ transporting, mitochondrial F1 complex, alpha subunit, isoform 1, cardiac muscle	ATP5A1	44928	44928	44928	44928	77	44852	191	>100	77
406	226276 _at	BF439522	hypothetical protein LOC153339	LOC153 339	44928	44928	77	44928	781	44148	909	>100	77
407	39313_ at	AB00234 2	protein kinase, lysine deficient 1	PRKWN K1	44928	44928	44928	44928	44850	79	343	>100	79
408	222109 _at	AA55858 3	hypothetical protein FLJ10613	FLJ1061 3	44928	44928	44928	79	44834	95	310	>100	79
409	211474 _s_at	BC004948 .1	serine (or cysteine) proteinase inhibitor, clade B (ovalbumin), member 6	SERPIN B6	44928	44928	44928	80	44692	237	648	>100	80
410	224915	AV75613	Homo sapiens, clone	---	89	44928	44928	44928	726	44203	1875	80	80

	_x_at	1	IMAGE:5285034, mRNA										
411	215528 _at	AL049390 .1	Homo sapiens mRNA; cDNA DKFZp586O1318 (from clone DKFZp586O1318)	---	44928	44928	44928	44928	44848	81	223	>100	81
412	222428 _s_at	D84223.1	leucyl-tRNA synthetase	LARS	44928	44928	81	44928	598	44331	1689	>100	81
413	232369 _at	AF339768 .1	Homo sapiens clone IMAGE:119716, mRNA sequence	---	44928	44928	44928	81	44430	499	864	>100	81
414	233849 _s_at	AK02301 4.1	Rho GTPase activating protein 5	ARHGAP5	81	44928	44928	44928	577	44352	1929	>100	81
415	204173 _at	NM_0024 75.1	myosin light chain 1 slow a	MLC1SA	44928	44928	44928	44928	82	44847	146	>100	82
416	213632 _at	M94065.1	dihydroorotate dehydrogenase	DHODH	44928	44928	44928	44928	44847	82	155	>100	82
417	225086 _at	BF679966	hypothetical protein FLJ38426	FLJ38426	83	44928	123	44928	408	44521	610	>100	83
418	225468 _at	AI761804	tripartite motif-containing 14	TRIM14	44928	44928	44928	44928	83	44846	136	>100	83
419	236617 _at	AW66308 3	Homo sapiens, clone IMAGE:5285945, mRNA	---	44928	44928	44928	83	44770	159	217	>100	83
420	210453 _x_at	AL050277 .1	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit g	ATP5L	84	44928	44928	44928	531	44398	1585	>100	84
421	216977 _x_at	AJ130972 .1	small nuclear ribonucleoprotein polypeptide A'	SNRPA1	44928	44928	44928	44928	84	44845	187	>100	84
422	237475 _x_at	AI151104	selenoprotein P, plasma, 1	SEPP1	44928	44928	44928	84	43126	1803	2926	>100	84

423	211794_at	AF198052.1	FYN binding protein (FYB-120/130)	FYB	44928	44928	44928	44928	44160	769	85	>100	85
424	201892_s_at	NM_000884.1	IMP (inosine monophosphate) dehydrogenase 2	IMPDH2	86	44928	44928	44928	3337	41592	14262	>100	86
425	218901_at	NM_020353.1	phospholipid scramblase 4	PLSCR4	44928	44928	44928	44928	44843	86	121	>100	86
426	241997_at	AA700817	ESTs, Weakly similar to hypothetical protein FLJ20234 [Homo sapiens] [H.sapiens]	---	44928	44928	44928	86	42689	2240	6135	>100	86
427	208463_at	NM_000809.1	gamma-aminobutyric acid (GABA) A receptor, alpha 4	GABRA4	44928	44928	44928	87	44731	198	377	>100	87
428	220071_x_at	NM_018097.1	hypothetical protein FLJ10460	FLJ10460	44928	44928	44928	91	44842	87	322	>100	87
429	222646_s_at	AW268365	ERO1-like (S. cerevisiae)	ERO1L	44928	44928	44928	44928	87	44842	150	>100	87
430	234875_at	AJ224082	---	---	44928	44928	87	44928	845	44084	2407	>100	87
431	207300_s_at	NM_000131.2	coagulation factor VII (serum prothrombin conversion accelerator)	F7	44928	44928	44928	44928	44782	147	88	>100	88
432	209083_at	U34690.1	coronin, actin binding protein, 1A	CORO1A	88	44928	44928	44928	7864	37065	30105	>100	88
433	216644_at	AK000185.1	Homo sapiens cDNA FLJ20178 fis, clone COL09990.	---	44928	44928	44928	44928	44841	88	270	>100	88
434	218920_at	NM_019057.1	hypothetical protein FLJ10404	FLJ10404	44928	44928	44928	88	44757	172	446	>100	88
435	224518_s_at	BC006436.1	hypothetical protein MGC13105	MGC13105	44928	44928	88	44928	450	44479	1018	>100	88
436	227916_x_at	AA747303	exosome component Rrp40	RRP40	44928	44928	44928	44928	88	44841	227	>100	88

437	202232_s_at	NM_006360.1	dendritic cell protein	GA17	44928	44928	44928	44928	89	44840	254	>100	89
438	215916_at	AL157418.1	misshapen/NIK-related kinase	MINK	44928	44928	44928	44928	44840	89	402	>100	89
439	228818_at	BF110792	Homo sapiens cDNA FLJ12727 fis, clone NT2RP2000027.	---	44928	44928	44928	89	43849	1080	3023	>100	89
440	200903_s_at	NM_000687.1	S-adenosylhomocysteine hydrolase	AHCY	44928	44928	90	44928	142	44787	237	97	90
441	206790_s_at	NM_004545.1	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1, 7kDa	NDUFB1	126	44928	92	44928	352	44577	1766	90	90
442	208013_s_at	NM_020115.1	acrosomal vesicle protein 1	ACRV1	44928	44928	44928	44928	44839	90	162	>100	90
443	224254_x_at	AF116695.1	---	---	44928	44928	44928	90	42695	2234	2842	>100	90
444	201825_s_at	AL572542	CGI-49 protein	CGI-49	91	44928	44928	44928	921	44008	4114	>100	91
445	204795_at	NM_025263.1	CAT56 protein	CAT56	44928	44928	44928	44928	91	44838	256	>100	91
446	218332_at	NM_018476.1	brain expressed, X-linked 1	BEX1	44928	44928	44928	44928	44838	91	201	>100	91
447	222975_s_at	AB020692.1	NRAS-related gene	D1S155E	44928	44928	113	44928	119	44810	177	91	91
448	215806_x_at	M13231.1	T cell receptor gamma constant 2	TRGC2	44928	44928	44928	44928	44837	92	321	>100	92
449	200037_s_at	NM_016587.1	chromobox homolog 3 (HP1 gamma homolog, Drosophila)	CBX3	44928	44928	135	44928	233	44696	448	92	92
450	225892_at	BF438417	Homo sapiens mRNA; cDNA DKFZp564D1164 (from clone DKFZp564D1164)	---	44928	44928	108	44928	92	44837	164	>100	92

451	209786_at	BC001282.1	high mobility group nucleosomal binding domain 4	HMGN4	44928	44928	44928	44928	267	44662	484	93	93
452	215056_at	AI267546	ESTs	---	44928	44928	44928	44928	44836	93	160	>100	93
453	223433_at	AF226046.1	GK003 protein	GK003	44928	44928	44928	44928	93	44836	122	>100	93
454	225304_s_at	BE741920	NADH-ubiquinone oxidoreductase subunit B14.7	NDUFA11	44928	44928	152	44928	146	44783	93	>100	93
455	234462_at	S51397	---	---	93	44928	44928	44928	4340	40589	28484	>100	93
456	205119_s_at	NM_002029.1	formyl peptide receptor 1	FPR1	44928	44928	44928	44928	44835	94	257	>100	94
457	224872_at	AB040896.1	KIAA1463 protein	KIAA1463	44928	44928	44928	44928	94	44835	451	>100	94
458	224952_at	BF115054	putative ankyrin-repeat containing protein	DKFZP564D166	44928	44928	44928	94	43286	1643	7694	>100	94
459	226756_at	AA191741	Homo sapiens cDNA FLJ11436 fis, clone HEMBA1001213.	---	94	44928	44928	44928	776	44153	2397	>100	94
460	202250_s_at	NM_015726.1	H326	H326	44928	44928	44928	95	42923	2006	6207	>100	95
461	223334_at	AL136941.1	hypothetical protein DKFZp586C1924	DKFZp586C1924	44928	44928	95	44928	240	44689	704	>100	95
462	226789_at	W84421	Human S6 H-8 mRNA expressed in chromosome 6-suppressed melanoma cells.	---	95	44928	44928	44928	2994	41935	15082	>100	95
463	208742_s_at	U78303.1	sin3-associated polypeptide, 18kDa	SAP18	44928	44928	44928	44928	242	44687	599	96	96
464	231810_at	BG106919	BRI3 binding protein	BRI3BP	96	44928	44928	44928	929	44000	3396	>100	96

465	244495_x_at	AL521157	hypothetical protein MGC11386	MGC11386	44928	44928	44928	96	41892	3037	4559	>100	96
466	205260_s_at	NM_001107.1	acylphosphatase 1, erythrocyte (common) type	ACYP1	44928	44928	44928	44928	136	44793	97	>100	97
467	213746_s_at	AW05185 6	filamin A, alpha (actin binding protein 280)	FLNA	97	44928	44928	44928	4383	40546	25901	>100	97
468	215601_at	AK02389 5.1	---	---	44928	44928	44928	44928	44832	97	932	>100	97
469	202565_s_at	NM_003174.2	supervillin	SVIL	98	44928	44928	44928	8543	36386	44011	>100	98
470	209596_at	AF245505 .1	adlican	DKFZp564I1922	44928	44928	44928	44928	44831	98	239	>100	98
471	225470_at	AL529634	mitotic phosphoprotein 44	LOC129401	44928	44928	44928	44928	98	44831	265	>100	98
472	243450_at	T40707	ESTs	---	44928	44928	44928	98	36175	8754	15508	>100	98
473	209036_s_at	BC001917 .1	malate dehydrogenase 2, NAD (mitochondrial)	MDH2	44928	44928	44928	44928	100	44829	258	>100	100
474	216380_x_at	AC00501 1	---	---	100	44928	131	44928	1371	43558	4699	>100	100
475	236646_at	BE301029	hypothetical protein FLJ31166	FLJ31166	44928	44928	44928	100	40827	4102	1539	>100	100

[00230] A Cox proportional hazard analysis was performed to determine predictors of time until disease progression (TTP) in patients with relapsed and refractory multiple myeloma after treatment with bortezomib. This methodology is designed to analyze time to event data where some of the data may be censored (see E.T. Lee, Statistical Methods for Survival Data Analysis, 2nd ed. 1992, John Wiley& Sons, Inc.). The statistical package SAS was used to perform the analysis. We first examined clinical and prognostic factors to identify which combination of factors showed the greatest association with TTP. This was accomplished by use of the score method for best subset selection. This method provides score chi-squared statistics for all possible model sizes ranging from one predictor to the total number of explanatory variables under consideration. Thus, the method first provides the best single predictor models in order of the highest chi-squared statistics. If there are significant single predictor models ($p < 0.05$), the procedure goes on to the next step of estimating all two predictor models and ranking them by the highest chi-squared statistic.

[00231] To assess if a 2 predictor model is a better fit than a single predictor model, the difference in the chi-squared statistics is calculated. This is a one degree of freedom chi-square test and can be assessed for statistical significance. If the difference proves to be significant at $p < 0.05$, we conclude the two predictor model is a better fit, the second variable is significantly associated with TTP after taking into account the first variable, and the process continues by estimating all three predictor models. The three predictor model is compared to the two predictor model in the same way as the two predictor model was assessed against the single predictor model. This process is continued until the difference chi-square test fails, that is $p > 0.05$ for adding in an additional variable to the model. By using this process, we found that the best model contained 3 significant prognostic or clinical factors, abnormal cytogentics, β2-microglobulin, and c-reactive protein. We defined this as our best prognostic variable model.

[00232] The next step was to determine if there were any genomic markers that were significantly associated with TTP after accounting for the prognostic factors. We first filtered the genomic data set, made up of some 44,000 transcripts from the Affymetrics U133A and U133B human array chips, to those genes which had at least one present call using the Affymetrix detection system for determining if a transcript is reliably detected or not. This left 13,529 transcripts for analysis. We then estimated Cox proportional hazard models for each of the 13,529 transcripts where each model also contained the 3 prognostic factors discussed above. That is, 13,529 models were estimated where each model

contained 1 transcript and the three prognostic factors. From each model, we obtained estimates of relative risk, 95% confidence intervals and p values for the association of each transcript to TTP. From the 13,529 models, we found 834 transcripts which had p values of less than 0.05. That is, we found 834 transcripts that were significantly and independently, from the prognostic factors, associated with TTP. These are listed in Table 2

[00233] **TABLE 2 Predictive markers Associated with Time to Disease Progression (TTP)**

No.	Probe set ID	Seq. Derived From (RefSeq/Genbank Accession)	Title	Gene Symbol	Hazard
83	201575_at	NM_012245.1	SKI-interacting protein	SNW1	>1
81	202647_s_at	NM_002524.2	neuroblastoma RAS viral (v-ras) oncogene homolog	NRAS	>1
234	203058_s_at	AW299958	3'-phosphoadenosine 5'-phosphosulfate synthase 2	PAPSS2	<1
42	203753_at	NM_003199.1	transcription factor 4	TCF4	<1
415	204173_at	NM_002475.1	myosin light chain 1 slow a	MLC1SA	>1
191	206121_at	NM_000036.1	adenosine monophosphate deaminase 1 (isoform M)	AMPD1	>1
404	208690_s_at	BC000915.1	PDZ and LIM domain 1 (elfin)	PDLIM1	>1
53	210993_s_at	U54826.1	MAD, mothers against decapentaplegic homolog 1 (Drosophila)	MADH1	>1
305	212110_at	D31887.1	KIAA0062 protein	KIAA0062	<1
41	212382_at	AK021980.1	Homo sapiens cDNA FLJ11918 fis, clone HEMBB1000272.	---	<1
43	212386_at	AK021980.1	Homo sapiens cDNA FLJ11918 fis, clone HEMBB1000272.	---	<1
40	212387_at	AK021980.1	Homo sapiens cDNA FLJ11918 fis, clone HEMBB1000272.	---	<1
467	213746_s_at	AW051856	filamin A, alpha (actin binding protein 280)	FLNA	>1
39	213891_s_at	AI927067	Homo sapiens cDNA FLJ11918 fis, clone HEMBB1000272.	---	<1
78	215744_at	AW514140	fusion, derived from t(12;16) malignant liposarcoma	FUS	<1
77	218319_at	NM_020651.2	pellino homolog 1 (Drosophila)	PELI1	<1
201	219429_at	NM_024306.1	fatty acid hydroxylase	FAAH	<1
126	222762_x_at	AU144259	LIM domains containing 1	LIMD1	>1
376	222789_at	BE888593	hypothetical protein FLJ11220	FLJ11220	>1
341	225373_at	BE271644	PP2135 protein	PP2135	<1
209	225710_at	H99792	Homo sapiens cDNA FLJ34013 fis, clone FCBBF2002111.	---	<1

48	227798_at	AU146891	EST	---	>1
464	231810_at	BG106919	BRI3 binding protein	BRI3BP	>1
76	232213_at	AU147506	pellino homolog 1 (Drosophila)	PELI1	<1
75	232304_at	AK026714.1	pellino homolog 1 (Drosophila)	PELI1	<1
224	235875_at	BF510711	EST	---	<1
172	242903_at	AI458949	EST	---	<1
476	222788_s_at	BE888593	hypothetical protein FLJ11220	FLJ11220	>1
477	213305_s_at	L42375.1	protein phosphatase 2, regulatory subunit B (B56), gamma isoform	PPP2R5C	>1
478	204774_at	NM_014210.1	ecotropic viral integration site 2A	EVI2A	<1
479	200984_s_at	NM_000611.1	CD59 antigen p18-20 (antigen identified by monoclonal antibodies 16.3A5, EJ16, EJ30, EL32 and G344)	CD59	<1
480	208956_x_at	U62891.1	dUTP pyrophosphatase	DUT	>1
481	216326_s_at	AF059650	histone deacetylase 3	HDAC3	<1
482	203845_at	AV727449	p300/CBP-associated factor	PCAF	<1
483	214349_at	AV764378	Homo sapiens cDNA: FLJ23438 fis, clone HRC13275.	---	>1
484	202332_at	NM_001894.1	casein kinase 1, epsilon	CSNK1E	>1
485	201020_at	NM_003405.1	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta polypeptide	YWHAH	<1
486	200612_s_at	NM_001282.1	adaptor-related protein complex 2, beta 1 subunit	AP2B1	<1
487	212612_at	D31888.1	REST corepressor	RCOR	>1
488	202963_at	AW027312	regulatory factor X, 5 (influences HLA class II expression)	RFX5	<1
489	212463_at	BE379006	Homo sapiens mRNA; cDNA DKFZp564J0323 (from clone DKFZp564J0323)	---	<1
490	202453_s_at	NM_005316.1	general transcription factor IIH, polypeptide 1, 62kDa	GTF2H1	<1
491	209239_at	M55643.1	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (p105)	NFKB1	<1
492	213405_at	N95443	Homo sapiens, clone IMAGE:4831050, mRNA	---	<1
493	200679_x_at	BE311760	high-mobility group box 1	HMGB1	>1

494	205981_s_at	NM_001564.1	inhibitor of growth family, member 1-like	ING1L	>1
495	211783_s_at	BC006177.1	metastasis associated 1	MTA1	>1
496	227482_at	AI097656	hypothetical protein LOC57143	LOC57143	>1
497	214943_s_at	D38491.1	KIAA0117 protein	KIAA0117	>1
498	205504_at	NM_000061.1	Bruton agammaglobulinemia tyrosine kinase	BTK	<1
499	218216_x_at	NM_016638.1	ADP-ribosylation-like factor 6 interacting protein 4	ARL6IP4	>1
500	221014_s_at	NM_031296.1	RAB33B, member RAS oncogene family	RAB33B	<1
501	202408_s_at	NM_015629.1	PRP31 pre-mRNA processing factor 31 homolog (yeast)	PRPF31	>1
502	217996_at	AA576961	pleckstrin homology-like domain, family A, member 1	PHLDA1	>1
503	229723_at	BF591040	T-cell activation GTPase activating protein	TAGAP	<1
504	227112_at	AW270037	KIAA0779 protein	KIAA0779	<1
505	218224_at	NM_006029.2	paraneoplastic antigen MA1	PNMA1	>1
506	213415_at	AI768628	chloride intracellular channel 2	CLIC2	<1
507	225251_at	AK021761.1	Homo sapiens cDNA FLJ11699 fis, clone HEMBA1005047, highly similar to RAS-RELATED PROTEIN RAB-24.	RAB24	<1
508	219228_at	NM_018555.2	zinc finger protein 463	ZNF463	<1
509	226979_at	AI125541	mitogen-activated protein kinase kinase kinase 2	MAP3K2	<1
510	227179_at	AK002152.1	staufen, RNA binding protein, homolog 2 (Drosophila)	STAU2	>1
511	205621_at	NM_006020.1	alkB, alkylation repair homolog (E. coli)	ALKBH	>1
512	226421_at	AA707320	hypothetical protein LOC286505	LOC286505	<1
513	219709_x_at	NM_023933.1	hypothetical protein MGC2494	MGC2494	>1
514	217803_at	NM_022130.1	golgi phosphoprotein 3 (coat-protein)	GOLPH3	<1
515	228980_at	AI760772	fring	LOC117584	<1
516	243020_at	R06738	EST	---	>1
517	211289_x_at	AF067524.1	cell division cycle 2-like 2	CDC2L2	>1

518	213137_s_at	AI828880	protein tyrosine phosphatase, non-receptor type 2	PTPN2	>1
519	204407_at	AF080255.1	transcription termination factor, RNA polymerase II	TTF2	>1
520	224938_at	AU144387	EST	---	<1
521	225466_at	AI761804	tripartite motif-containing 14	TRIM14	<1
522	208908_s_at	AF327443.1	calpastatin	CAST	<1
523	222343_at	AA629050	Homo sapiens full length insert cDNA clone ZA94C02	---	>1
524	224566_at	AK027191.1	Homo sapiens cDNA: FLJ23538 fis, clone LNG08010, highly similar to BETA2 Human MEN1 region clone epsilon/beta mRNA.	---	<1
525	208297_s_at	NM_005665.1	---	---	>1
526	213923_at	AW005535	RAP2B, member of RAS oncogene family	RAP2B	<1
527	228680_at	AW340096	EST, Moderately similar to hypothetical protein FLJ20489 [Homo sapiens] [H.sapiens]	---	<1
528	209204_at	AI824831	LIM domain only 4	LMO4	>1
529	208093_s_at	NM_030808.1	LIS1-interacting protein NUDEL; endooligopeptidase A	NUDEL	<1
530	200982_s_at	NM_001155.2	annexin A6	ANXA6	<1
531	218249_at	NM_022494.1	zinc finger, DHHC domain containing 6	ZDHHC6	<1
532	203345_s_at	AI566096	likely ortholog of mouse metal response element binding transcription factor 2	M96	>1
533	223141_at	AK022317.1	uridine-cytidine kinase 1	UCK1	>1
534	222444_at	AL121883	ALEX3 protein	ALEX3	<1
535	217853_at	NM_022748.1	tumor endothelial marker 6	TEM6	<1
536	220244_at	NM_013343.1	NAG-7 protein	NAG-7	<1
537	213995_at	AW195882	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit s (factor B)	ATP5S	>1
538	214072_x_at	AA679297	secreted protein of unknown function	SPUF	>1
539	200950_at	NM_006409.1	actin related protein 2/3 complex, subunit 1A, 41kDa	ARPC1A	<1

540	224878_at	N63936	similar to ubiquitin binding protein	UBPH	>1
541	227294_at	AI474448	hypothetical protein BC014000	LOC115509	>1
542	214334_x_at	N34846	DAZ associated protein 2	DAZAP2	>1
543	214659_x_at	AC007956	ZAP3 protein	ZAP3	>1
544	36499_at	D87469	cadherin, EGF LAG seven-pass G-type receptor 2 (flamingo homolog, Drosophila)	CELSR2	>1
545	229512_at	BE464337	EST	---	>1
546	206662_at	NM_002064.1	glutaredoxin (thioltransferase)	GLRX	<1
547	200914_x_at	BF589024	kinectin 1 (kinesin receptor)	KTN1	>1
548	214938_x_at	AF283771.2	high-mobility group box 1	HMGB1	>1
549	203243_s_at	NM_006457.1	LIM protein (similar to rat protein kinase C-binding enigma)	LIM	<1
550	214395_x_at	AI335509	eukaryotic translation elongation factor 1 delta (guanine nucleotide exchange protein)	EEF1D	>1
551	217208_s_at	AL121981	discs, large (Drosophila) homolog 1	DLG1	>1
552	224180_x_at	AF131737.1	hypothetical protein LOC51057	LOC51057	>1
553	218724_s_at	NM_021809.1	TGFB-induced factor 2 (TALE family homeobox)	TGIF2	<1
554	210387_at	BC001131.1	histone 1, H2bg	HIST1H2BG	>1
555	208898_at	AF077614.1	ATPase, H+ transporting, lysosomal 34kDa, V1 subunit D	ATP6V1D	>1
556	200645_at	NM_007278.1	GABA(A) receptor-associated protein	GABARAP	<1
557	200985_s_at	NM_000611.1	CD59 antigen p18-20 (antigen identified by monoclonal antibodies 16.3A5, EJ16, EJ30, EL32 and G344)	CD59	<1
558	220595_at	NM_013377.1	hypothetical protein DKFZp434B0417	DKFZp434B0417	>1
559	236550_s_at	BF508689	Homo sapiens mRNA; cDNA DKFZp686I2118 (from clone DKFZp686I2118)	ZNF311	>1

560	202279_at	NM_004894.1	chromosome 14 open reading frame 2	C14orf2	>1
561	234312_s_at	AK000162.1	acetyl-Coenzyme A synthetase 2 (ADP forming)	ACAS2	>1
562	213945_s_at	AI867102	nucleoporin 210	NUP210	>1
563	228380_at	BE551193	EST, Weakly similar to hypothetical protein FLJ20378 [Homo sapiens] [H.sapiens]	---	<1
564	203574_at	NM_005384.1	nuclear factor, interleukin 3 regulated	NFIL3	>1
565	222146_s_at	AK026674.1	transcription factor 4	TCF4	<1
566	227665_at	BE968576	Homo sapiens, clone IMAGE:4152387, mRNA	---	<1
567	207995_s_at	NM_014257.1	CD209 antigen-like	CD209L	<1
568	201097_s_at	NM_001660.2	ADP-ribosylation factor 4	ARF4	<1
569	203975_s_at	BF000239	chromatin assembly factor 1, subunit A (p150)	CHAF1A	>1
570	209136_s_at	BG390445	ubiquitin specific protease 10	USP10	>1
571	238086_at	AI288372	EST	---	>1
572	242388_x_at	AW576600	EST	---	<1
573	241876_at	AW663060	EST	---	<1
574	228195_at	BE645119	EST	---	<1
575	202334_s_at	AA877765	ubiquitin-conjugating enzyme E2B (RAD6 homolog)	UBE2B	<1
576	201472_at	NM_003372.2	von Hippel-Lindau binding protein 1	VBP1	<1
577	217092_x_at	AL031589	---	---	>1
578	208744_x_at	BG403660	heat shock 105kDa/110kDa protein 1	HSPH1	>1
579	212412_at	AV715767	Homo sapiens mRNA; cDNA DKFZp564A072 (from clone DKFZp564A072)	---	<1
580	217995_at	NM_021199.1	sulfide quinone reductase-like (yeast)	SQRDL	<1
581	203275_at	NM_002199.2	interferon regulatory factor 2	IRF2	<1
582	207335_x_at	NM_007100.1	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit e	ATP5I	>1
583	218130_at	NM_024510.1	hypothetical protein MGC4368	MGC4368	>1

584	208914_at	NM_015044.1	golgi associated, gamma adaptin ear containing, ARF binding protein 2	GGA2	<1
585	202985_s_at	NM_004873.1	BCL2-associated athanogene 5	BAG5	>1
586	206587_at	NM_006584.1	chaperonin containing TCP1, subunit 6B (zeta 2)	CCT6B	<1
587	223419_at	BC004290.1	hypothetical protein MGC10870	MGC10870	>1
588	213102_at	Z78330	ARP3 actin-related protein 3 homolog (yeast)	ACTR3	<1
589	226520_at	AI831506	EST	---	<1
590	201366_at	NM_004034.1	annexin A7	ANXA7	<1
591	213021_at	AI741876	Homo sapiens mRNA; cDNA DKFZp566B213 (from clone DKFZp566B213)	---	<1
592	201172_x_at	NM_003945.1	ATPase, H+ transporting, lysosomal 9kDa, V0 subunit e	ATP6V0E	<1
593	213295_at	AA555096	Homo sapiens mRNA; cDNA DKFZp586D1122 (from clone DKFZp586D1122)	---	<1
594	226406_at	AI823360	hypothetical protein MGC12909	MGC12909	<1
595	210564_x_at	AF009619.1	CASP8 and FADD-like apoptosis regulator	CFLAR	<1
596	242606_at	AL043482	EST	---	<1
597	203292_s_at	NM_021729.2	vacuolar protein sorting 11 (yeast)	VPS11	>1
598	202579_x_at	NM_006353.1	high mobility group nucleosomal binding domain 4	HMGN4	<1
599	229113_s_at	W16779	protein kinase C, zeta	PRKCZ	>1
600	244743_x_at	AA114243	zinc finger protein 138 (clone pHZ-32)	ZNF138	<1
601	222622_at	BG284709	hypothetical protein LOC283871	LOC283871	>1
602	210312_s_at	BC002640.1	hypothetical protein LOC90410	LOC90410	<1
603	221530_s_at	AB044088.1	basic helix-loop-helix domain containing, class B, 3	BHLHB3	<1
604	201994_at	NM_012286.1	mortality factor 4 like 2	MORF4L2	<1
605	227262_at	BE348293	Homo sapiens proteoglycan link protein mRNA, complete cds.	---	>1

606	203693_s_at	NM_001949.2	E2F transcription factor 3	E2F3	<1
607	221750_at	BG035985	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 1 (soluble)	HMGCS1	<1
608	214789_x_at	AA524274	Splicing factor, arginine/serine-rich, 46kD	SRP46	<1
609	200761_s_at	NM_006407.2	vitamin A responsive; cytoskeleton related	JWA	<1
610	212233_at	AL523076	Homo sapiens cDNA FLJ30550 fis, clone BRAWH2001502.	---	<1
611	209300_s_at	BC002888.1	DKFZP566B183 protein	DKFZP566B 183	<1
612	213708_s_at	N40555	transcription factor-like 4	TCFL4	<1
613	207467_x_at	NM_001750.2	calpastatin	CAST	<1
614	225414_at	AL558987	hypothetical protein LOC284996	LOC284996	<1
615	235104_at	BG292389	EST	---	<1
616	214003_x_at	BF184532	ribosomal protein S20	RPS20	>1
617	201542_at	AY008268.1	SAR1 protein	SAR1	<1
618	211316_x_at	AF009616.1	CASP8 and FADD-like apoptosis regulator	CFLAR	<1
619	221522_at	AL136784.1	hypothetical protein DKFZp434L0718	DKFZP434L 0718	<1
620	210844_x_at	D14705.1	catenin (cadherin-associated protein), alpha 1, 102kDa	CTNNA1	<1
621	210448_s_at	U49396.1	purinergic receptor P2X, ligand-gated ion channel, 5	P2RX5	<1
622	212843_at	AA126505	neural cell adhesion molecule 1	NCAM1	<1
623	224284_x_at	AF338193.1	---	---	>1
624	222650_s_at	BE898559	SLC2A4 regulator	SLC2A4RG	>1
625	212719_at	AB011178.1	pleckstrin homology domain containing, family E (with leucine rich repeats) member 1	PLEKHE1	>1
626	38069_at	Z67743	chloride channel 7	CLCN7	>1
627	233625_x_at	AK021939.1	hypothetical protein FLJ20542	FLJ20542	>1

628	205053_at	NM_000946.1	primase, polypeptide 1, 49kDa	PRIM1	>1
629	239749_at	AW205090	EST	---	>1
630	34764_at	D21851	leucyl-tRNA synthetase, mitochondrial	LARS2	>1
631	205659_at	NM_014707.1	histone deacetylase 9	HDAC9	<1
632	242092_at	AA019300	EST, Moderately similar to hypothetical protein FLJ20097 [Homo sapiens] [H.sapiens]	---	>1
633	203575_at	NM_001896.1	casein kinase 2, alpha prime polypeptide	CSNK2A2	>1
634	221297_at	NM_018654.1	G protein-coupled receptor, family C, group 5, member D	GPRC5D	<1
635	212900_at	BE645231	SEC24 related gene family, member A (S. cerevisiae)	SEC24A	<1
636	230036_at	BE669858	hypothetical protein FLJ39885	FLJ39885	<1
637	213101_s_at	Z78330	ARP3 actin-related protein 3 homolog (yeast)	ACTR3	<1
638	222846_at	AB038995.1	RAB-8b protein	LOC51762	<1
639	213455_at	W87466	pleckstrin homology domain containing, family B (evectins) member 2	PLEKHB2	<1
640	242613_at	AI809536	EST	---	>1
641	218206_x_at	NM_016558.1	SCAN domain containing 1	SCAND1	>1
642	222014_x_at	AI249752	MTO1 protein	MTO1	<1
643	212219_at	D38521.1	proteasome activator 200 kDa	PA200	<1
644	219806_s_at	NM_020179.1	FN5 protein	FN5	<1
645	218875_s_at	NM_012177.1	F-box only protein 5	FBXO5	>1
646	208485_x_at	NM_003879.1	CASP8 and FADD-like apoptosis regulator	CFLAR	<1
647	218233_s_at	NM_017601.1	chromosome 6 open reading frame 49	C6orf49	>1
648	214130_s_at	AI821791	phosphodiesterase 4D interacting protein (myomegalin)	PDE4DIP	<1
649	208723_at	BC000350.1	ubiquitin specific protease 11	USP11	>1
650	217814_at	NM_020198.1	GK001 protein	GK001	<1
651	208809_s_at	AL136632.1	hypothetical protein FLJ12619	FLJ12619	>1

652	201199_s_at	NM_002807.1	proteasome (prosome, macropain) 26S subunit, non-ATPase, 1	PSMD1	<1
653	242937_at	AV763408	EST, Moderately similar to ILF1_HUMAN Interleukin enhancer-binding factor 1 (Cellular transcription factor ILF-1) [H.sapiens]	---	>1
654	212333_at	AL049943.1	DKFZP564F0522 protein	DKFZP564F0522	<1
655	210817_s_at	BC004130.1	nuclear domain 10 protein	NDP52	<1
656	212508_at	AK024029.1	modulator of apoptosis 1	MOAP1	>1
657	213603_s_at	BE138888	ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)	RAC2	<1
658	233274_at	AU145144	---	---	>1
659	218557_at	NM_020202.1	Nit protein 2	NIT2	<1
660	231428_at	BE502947	EST	---	<1
661	201810_s_at	AL562152	SH3-domain binding protein 5 (BTK-associated)	SH3BP5	<1
662	209970_x_at	M87507.1	caspase 1, apoptosis-related cysteine protease (interleukin 1, beta, convertase)	CASP1	<1
663	208965_s_at	BG256677	interferon, gamma-inducible protein 16	IFI16	>1
664	203038_at	NM_002844.1	protein tyrosine phosphatase, receptor type, K	PTPRK	<1
665	202442_at	NM_001284.1	adaptor-related protein complex 3, sigma 1 subunit	AP3S1	<1
666	209515_s_at	U38654.3	RAB27A, member RAS oncogene family	RAB27A	<1
667	201865_x_at	AI432196	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	NR3C1	<1
668	204786_s_at	L41944.1	interferon (alpha, beta and omega) receptor 2	IFNAR2	>1
669	209508_x_at	AF005774.1	CASP8 and FADD-like apoptosis regulator	CFLAR	<1
670	200822_x_at	NM_000365.1	triosephosphate isomerase 1	TPI1	>1
671	217322_x_at	AL024509	---	---	>1
672	203505_at	AF285167.1	ATP-binding cassette, sub-family A (ABC1), member 1	ABCA1	>1

673	223347_at	AL360266.1	hypothetical protein FLJ22283	FLJ22283	>1
674	209765_at	Y13786.2	a disintegrin and metalloproteinase domain 19 (meltrin beta)	ADAM19	<1
675	202972_s_at	AW450403	family with sequence similarity 13, member A1	FAM13A1	>1
676	203380_x_at	NM_006925.1	splicing factor, arginine/serine-rich 5	SFRS5	>1
677	212211_at	AI986295	gene trap ankyrin repeat	GTAR	<1
678	218326_s_at	NM_018490.1	G protein-coupled receptor 48	GPR48	>1
679	217994_x_at	NM_017871.1	hypothetical protein FLJ20542	FLJ20542	>1
680	239835_at	AA669114	T-cell activation kelch repeat protein	TA-KRP	<1
681	213353_at	BF693921	ATP-binding cassette, sub-family A (ABC1), member 5	ABCA5	<1
682	208710_s_at	AI424923	adaptor-related protein complex 3, delta 1 subunit	AP3D1	>1
683	205011_at	NM_014622.1	loss of heterozygosity, 11, chromosomal region 2, gene A	LOH11CR2A	<1
684	202027_at	NM_012264.1	chromosome 22 open reading frame 5	C22orf5	>1
685	203642_s_at	NM_014900.1	KIAA0977 protein	KIAA0977	<1
686	212266_s_at	AW084582	splicing factor, arginine/serine-rich 5	SFRS5	>1
687	238693_at	AA165136	EST	---	<1
688	219342_at	NM_022900.1	O-acetyltransferase	CAS1	<1
689	201769_at	NM_014666.1	enthoprotin	ENTH	<1
690	243982_at	AA455180	EST, Weakly similar to KHLX_HUMAN Kelch-like protein X [H.sapiens]	---	>1
691	230490_x_at	AI866717	hypothetical protein FLJ31034	FLJ31034	<1
692	227073_at	N50665	Homo sapiens cDNA FLJ36574 fis, clone TRACH2012376.	---	<1
693	226858_at	T51255	chromosome 1 open reading frame 28	C1orf28	>1
694	219759_at	NM_022350.1	aminopeptidase	LOC64167	<1
695	208325_s_at	NM_006738.1	A kinase (PRKA) anchor protein 13	AKAP13	>1
696	212053_at	AK025504.1	KIAA0251 protein	KIAA0251	<1
697	222715_s_at	BE856321	AP1 gamma subunit binding protein 1	AP1GBP1	<1

698	235456_at	AI810266	Homo sapiens, clone IMAGE:4819084, mRNA	---	>1
699	235424_at	N66727	EST	---	<1
700	212407_at	AL049669.1	CGI-01 protein	CGI-01	<1
701	227565_at	BE501881	EST	---	<1
702	228091_at	AI800609	EST, Weakly similar to D29149 proline-rich protein - mouse (fragment) [M.musculus]	---	>1
703	209258_s_at	NM_005445.1	chondroitin sulfate proteoglycan 6 (bamacan)	CSPG6	>1
704	222590_s_at	AF180819.1	nemo-like kinase	NLK	<1
705	212528_at	AL023553	Homo sapiens, clone IMAGE:3605655, mRNA	---	<1
706	203981_s_at	AL574660	ATP-binding cassette, sub-family D (ALD), member 4	ABCD4	>1
707	201011_at	NM_002950.1	ribophorin I	RPN1	<1
708	244268_x_at	BF435769	EST, Weakly similar to hypothetical protein FLJ20378 [Homo sapiens] [H.sapiens]	---	<1
709	202315_s_at	NM_004327.2	breakpoint cluster region	BCR	<1
710	227698_s_at	AW007215	RAB40C, member RAS oncogene family	RAB40C	>1
711	218311_at	NM_003618.1	mitogen-activated protein kinase kinase kinase kinase 3	MAP4K3	<1
712	213931_at	AI819238	inhibitor of DNA binding 2, dominant negative helix-loop-helix protein	ID2	>1
713	217997_at	AA576961	pleckstrin homology-like domain, family A, member 1	PHLDA1	>1
714	208951_at	BC002515.1	aldehyde dehydrogenase 7 family, member A1	ALDH7A1	>1
715	225847_at	AB037784.1	KIAA1363 protein	KIAA1363	<1
716	202846_s_at	NM_002642.1	phosphatidylinositol glycan, class C	PIGC	<1
717	200681_at	NM_006708.1	glyoxalase I	GLO1	<1
718	202727_s_at	NM_000416.1	interferon gamma receptor 1	IFNGR1	<1
719	222231_s_at	AK025328.1	hypothetical protein PRO1855	PRO1855	<1
720	228482_at	AV702789	hypothetical protein FLJ36674	FLJ36674	>1
721	235056_at	AV722693	EST	---	<1

722	202010_s_at	NM_021188.1	likely ortholog of mouse another partner for ARF 1	APA1	>1
723	226556_at	BF431260	Homo sapiens, clone IMAGE:4815204, mRNA	---	<1
724	215088_s_at	BG110532	EST, Highly similar to succinate dehydrogenase complex, subunit C precursor; Succinate dehydrogenase complex, subunit C, integral membrane protein,; succinate-ubiquinone oxidoreducatase cytochrome B large subunit [Homo sapiens] [H.sapiens]	---	>1
725	209492_x_at	BC003679.1	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit e	ATP5I	>1
726	211075_s_at	Z25521.1	CD47 antigen (Rh-related antigen, integrin-associated signal transducer)	CD47	<1
727	204552_at	AA355179	Homo sapiens cDNA FLJ34214 fis, clone FCBBF3021807.	---	<1
728	211862_x_at	AF015451.1	CASP8 and FADD-like apoptosis regulator	CFLAR	<1
729	201403_s_at	NM_004528.1	microsomal glutathione S-transferase 3	MGST3	<1
730	209899_s_at	AF217197.1	fuse-binding protein-interacting repressor	SIAHBP1	>1
731	219023_at	NM_018569.1	hypothetical protein PRO0971	PRO0971	>1
732	236506_at	BF507371	EST	---	>1
733	205191_at	NM_006915.1	retinitis pigmentosa 2 (X-linked recessive)	RP2	<1
734	202146_at	AA747426	interferon-related developmental regulator 1	IFRD1	<1
735	243304_at	AI733824	hypothetical protein LOC286109	LOC286109	>1
736	223658_at	AF134149.1	potassium channel, subfamily K, member 6	KCNK6	<1
737	202074_s_at	NM_021980.1	optineurin	OPTN	<1
738	203162_s_at	NM_005886.1	katanin p80 (WD40-containing) subunit B 1	KATNB1	>1
739	208841_s_at	AB014560.1	Ras-GTPase activating protein SH3 domain-binding protein 2	G3BP2	<1
740	230128_at	AK025231.1	Homo sapiens cDNA: FLJ21578 fis, clone COL06726.	---	<1
741	214394_x_at	AI613383	eukaryotic translation elongation factor 1 delta (guanine nucleotide exchange protein)	EEF1D	>1

742	242969_at	AI288679	EST	---	<1
743	210251_s_at	AF112221.1	rap2 interacting protein x	RIPX	>1
744	209894_at	U50748.1	leptin receptor	LEPR	<1
745	204190_at	NM_005800.1	highly charged protein	D13S106E	>1
746	202438_x_at	BF346014	Homo sapiens, clone IMAGE:5278680, mRNA	---	<1
747	211968_s_at	NM_005348.1	heat shock 90kDa protein 1, alpha	HSPCA	>1
748	222424_s_at	BC000805.1	similar to rat nuclear ubiquitous casein kinase 2	NUCKS	>1
749	226445_s_at	AI743109	tripartite motif-containing 41	TRIM41	>1
750	235061_at	AV706522	hypothetical protein DKFZp761G058	DKFZp761G058	<1
751	34031_i_at	U90268	cerebral cavernous malformations 1	CCM1	<1
752	213160_at	D86964.1	dedicator of cyto-kinesis 2	DOCK2	<1
753	209194_at	BC005334.1	centrin, EF-hand protein, 2	CETN2	<1
754	209240_at	AF070560.1	O-linked N-acetylglucosamine (GlcNAc) transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylglucosaminyl transferase)	OGT	<1
755	218962_s_at	NM_022484.1	hypothetical protein FLJ13576	FLJ13576	<1
756	203525_s_at	AI375486	adenomatosis polyposis coli	APC	<1
757	219904_at	NM_024303.1	hypothetical protein MGC4161	MGC4161	>1
758	205550_s_at	NM_004899.1	brain and reproductive organ-expressed (TNFRSF1A modulator)	BRE	<1
759	209932_s_at	U90223.1	dUTP pyrophosphatase	DUT	>1
760	AFFX-M27830_M_at	M27830	---	---	>1
761	205297_s_at	NM_000626.1	CD79B antigen (immunoglobulin-associated beta)	CD79B	<1
762	232297_at	AL049385.1	Homo sapiens mRNA; cDNA DKFZp586M1418 (from clone DKFZp586M1418)	---	<1

763	204019_s_at	NM_015677.1	likely ortholog of mouse Sh3 domain YSC-like 1	SH3YL1	<1
764	230769_at	AI916261	EST, Weakly similar to PRP1_HUMAN Salivary proline-rich protein precursor (Clones CP3, CP4 and CP5) [Contains: Basic peptide IB-6; Peptide P-H] [H.sapiens]	---	>1
765	217501_at	AI339732	Homo sapiens, clone IMAGE:5268928, mRNA	---	<1
766	205105_at	NM_002372.1	mannosidase, alpha, class 2A, member 1	MAN2A1	<1
767	209514_s_at	BE502030	RAB27A, member RAS oncogene family	RAB27A	<1
768	203217_s_at	NM_003896.1	sialyltransferase 9 (CMP-NeuAc:lactosylceramide alpha-2,3-sialyltransferase; GM3 synthase)	SIAT9	<1
769	203176_s_at	BE552470	transcription factor A, mitochondrial	TFAM	>1
770	208988_at	AK024505.1	F-box and leucine-rich repeat protein 11	FBXL11	<1
771	221500_s_at	AF008936.1	aminopeptidase-like 1	NPEPL1	>1
772	229236_s_at	AI346445	eukaryotic translation initiation factor 3, subunit 10 theta, 150/170kDa	EIF3S10	<1
773	218267_at	NM_016550.1	cyclin-dependent kinase 2-interacting protein	CINP	>1
774	208129_x_at	NM_001754.1	runt-related transcription factor 1 (acute myeloid leukemia 1; aml1 oncogene)	RUNX1	>1
775	208764_s_at	D13119.1	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c (subunit 9), isoform 2	ATP5G2	>1
776	225498_at	AV713673	chromosome 20 open reading frame 178	C20orf178	<1
777	211317_s_at	AF041461.1	CASP8 and FADD-like apoptosis regulator	CFLAR	<1
778	200760_s_at	N92494	vitamin A responsive; cytoskeleton related	JWA	<1
779	215483_at	AK000270.1	A kinase (PRKA) anchor protein (yotiao) 9	AKAP9	<1
780	218194_at	NM_015523.1	small fragment nuclease	DKFZP566E144	<1
781	201388_at	NM_002809.1	proteasome (prosome, macropain) 26S subunit, non-ATPase, 3	PSMD3	<1
782	34406_at	AB011174	KIAA0602 protein	KIAA0602	>1

783	208386_x_at	NM_007068.1	DMC1 dosage suppressor of mck1 homolog, meiosis-specific homologous recombination (yeast)	DMC1	>1
784	244481_at	BF196523	EST	---	>1
785	239673_at	AW080999	EST	---	<1
786	208773_s_at	AL136943.1	FLJ20288 protein	FLJ20288	<1
787	222206_s_at	AA781143	hypothetical protein from EUROIMAGE 2021883	LOC56926	>1
788	228658_at	R54042	Homo sapiens cDNA FLJ25887 fis, clone CBR02996.	---	<1
789	212586_at	BG111635	type 1 tumor necrosis factor receptor shedding aminopeptidase regulator	ARTS-1	<1
790	238011_at	BF668314	Homo sapiens cDNA FLJ37032 fis, clone BRACE2011265.	---	>1
791	204659_s_at	AF124604.1	growth factor, augmenter of liver regeneration (ERV1 homolog, S. cerevisiae)	GFER	>1
792	200096_s_at	AI862255	ATPase, H+ transporting, lysosomal 9kDa, V0 subunit e	ATP6V0E	<1
793	227293_at	AI264003	Homo sapiens cDNA FLJ34052 fis, clone FCBBF3000175.	---	<1
794	228454_at	AW663968	KIAA1795 protein	MLR2	<1
795	209576_at	AL049933.1	guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 1	GNAI1	<1
796	201684_s_at	BE783632	chromosome 14 open reading frame 92	C14orf92	>1
797	233068_at	AK023264.1	EST, Weakly similar to POL2_MOUSE Retrovirus-related POL polyprotein [Contains: Reverse transcriptase ; Endonuclease] [M.musculus]	---	<1
798	210532_s_at	AF116639.1	chromosome 14 open reading frame 2	C14orf2	>1
799	211911_x_at	L07950.1	major histocompatibility complex, class I, B	HLA-B	<1
800	208991_at	AA634272	Homo sapiens cDNA FLJ35646 fis, clone SPLEN2012743.	---	<1
801	226612_at	AW572911	Homo sapiens cDNA FLJ25076 fis, clone CBL06117.	---	<1
802	223068_at	AV707345	echinoderm microtubule associated protein like 4	EML4	<1
803	227462_at	BE889628	EST	---	<1
804	224680_at	AL539253	Homo sapiens, clone IMAGE:3866125, mRNA	---	<1

805	244075_at	BF224218	EST	---	>1
806	228220_at	AI627666	hypothetical protein BC014311	LOC115548	<1
807	225729_at	AI870857	Homo sapiens cDNA: FLJ21560 fis, clone COL06410.	---	<1
808	222771_s_at	NM_016132.1	myelin gene expression factor 2	MEF-2	<1
809	209944_at	BC000330.1	likely ortholog of mouse another partner for ARF 1	APA1	>1
810	224565_at	AK027191.1	Homo sapiens cDNA: FLJ23538 fis, clone LNG08010, highly similar to BETA2 Human MEN1 region clone epsilon/beta mRNA.	---	<1
811	202439_s_at	NM_000202.2	iduronate 2-sulfatase (Hunter syndrome)	IDS	<1
812	212051_at	AK026913.1	Homo sapiens cDNA FLJ30463 fis, clone BRACE2009517.	---	<1
813	211969_at	NM_005348.1	heat shock 90kDa protein 1, alpha	HSPCA	>1
814	218209_s_at	NM_018170.1	hypothetical protein FLJ10656	P15RS	<1
815	208877_at	AF092132.1	Homo sapiens, clone IMAGE:6058556, mRNA	---	<1
816	202043_s_at	NM_004595.1	spermine synthase	SMS	<1
817	209092_s_at	AF061730.1	CGI-150 protein	CGI-150	<1
818	225412_at	AA761169	hypothetical protein FLJ14681	FLJ14681	<1
819	201173_x_at	NM_006600.1	nuclear distribution gene C homolog (A. nidulans)	NUDC	>1
820	201409_s_at	NM_002709.1	protein phosphatase 1, catalytic subunit, beta isoform	PPP1CB	<1
821	235594_at	AL542578	EST, Weakly similar to cytokine receptor-like factor 2; cytokine receptor CRL2 precusor [Homo sapiens] [H.sapiens]	---	>1
822	218269_at	NM_013235.1	putative ribonuclease III	RNASE3L	>1
823	213892_s_at	AA927724	adenine phosphoribosyltransferase	APRT	>1
824	209715_at	L07515.1	chromobox homolog 5 (HP1 alpha homolog, Drosophila)	CBX5	>1
825	215001_s_at	AL161952.1	glutamate-ammonia ligase (glutamine synthase)	GLUL	<1
826	230011_at	AW195720	hypothetical protein MGC40042	MGC40042	<1
827	202623_at	NM_018453.1	chromosome 14 open reading frame 11	C14orf11	>1
828	226749_at	AL582429	Homo sapiens, clone IMAGE:4791565, mRNA	---	<1
829	209337_at	AF063020.1	PC4 and SFRS1 interacting protein 2	PSIP2	<1

830	216526_x_at	AK024836.1	major histocompatibility complex, class I, C	HLA-C	<1
831	212428_at	AB002366.1	KIAA0368 protein	KIAA0368	<1
832	222035_s_at	AI984479	poly(A) polymerase alpha	PAPOLA	>1
833	223277_at	BC000623.1	hypothetical protein FLJ20211	FLJ20211	>1
834	212807_s_at	BE742268	sortilin 1	SORT1	>1
835	212193_s_at	BE881529	likely ortholog of mouse la related protein	LARP	<1
836	238642_at	AW367571	Homo sapiens full length insert cDNA clone YB31A06	---	>1
837	216607_s_at	U40053	---	---	<1
838	224851_at	AW274756	Homo sapiens cDNA FLJ31360 fis, clone MESAN2000572.	---	<1
839	53202_at	AA402435	hypothetical protein MGC2821	MGC2821	<1
840	224435_at	BC005871.1	hypothetical protein MGC4248	MGC4248	<1
841	200953_s_at	NM_001759.1	cyclin D2	CCND2	<1
842	240237_at	H23230	EST, Moderately similar to hypothetical protein FLJ20489 [Homo sapiens] [H.sapiens]	---	<1
843	227801_at	N90779	EST, Weakly similar to hypothetical protein FLJ20378 [Homo sapiens] [H.sapiens]	---	<1
844	243217_at	AI681312	EST	---	<1
845	217742_s_at	NM_016628.1	WW domain-containing adapter with a coiled-coil region	WAC	<1
846	206472_s_at	NM_005078.1	transducin-like enhancer of split 3 (E(sp1) homolog, Drosophila)	TLE3	<1
847	219100_at	NM_024928.1	hypothetical protein FLJ22559	FLJ22559	<1
848	41856_at	AL049370	Homo sapiens mRNA; cDNA DKFZp586D0918 (from clone DKFZp586D0918)	---	>1
849	211921_x_at	AF348514.1	prothymosin, alpha (gene sequence 28)	PTMA	>1
850	220597_s_at	NM_018694.1	ADP-ribosylation-like factor 6 interacting protein 4	ARL6IP4	>1
851	202461_at	NM_014239.1	eukaryotic translation initiation factor 2B, subunit 2 beta, 39kDa	EIF2B2	>1
852	201734_at	NM_001829.1	Homo sapiens mRNA; cDNA DKFZp564I0463 (from clone DKFZp564I0463)	---	<1

853	200644_at	NM_023009.1	MARCKS-like protein	MLP	>1
854	223459_s_at	BE222214	hypothetical protein FLJ20519	FLJ20519	>1
855	219215_s_at	NM_017767.1	solute carrier family 39 (zinc transporter), member 4	SLC39A4	>1
856	201811_x_at	NM_004844.1	SH3-domain binding protein 5 (BTK-associated)	SH3BP5	<1
857	212264_s_at	D87450.1	friend of EBNA2	FOE	<1
858	218668_s_at	NM_021183.1	hypothetical protein similar to small G proteins, especially RAP-2A	LOC57826	<1
859	209418_s_at	BC003615.1	chromosome 22 open reading frame 19	C22orf19	>1
860	203028_s_at	NM_000101.1	cytochrome b-245, alpha polypeptide	CYBA	>1
861	219410_at	NM_018004.1	hypothetical protein FLJ10134	FLJ10134	<1
862	218220_at	NM_021640.1	chromosome 12 open reading frame 10	C12orf10	>1
863	213154_s_at	AB014599.1	coiled-coil protein BICD2	BICD2	>1
864	200920_s_at	AL535380	B-cell translocation gene 1, anti-proliferative	BTG1	>1
865	214459_x_at	M12679.1	Cw1 antigen	HUMMHCW 1A	<1
866	205955_at	NM_018336.1	hypothetical protein FLJ11136	FLJ11136	>1
867	218482_at	NM_020189.1	DC6 protein	DC6	>1
868	203159_at	NM_014905.1	glutaminase	GLS	<1
869	217823_s_at	NM_016021.1	ubiquitin-conjugating enzyme E2, J1 (UBC6 homolog, yeast)	UBE2J1	<1
870	225445_at	AI332346	EST	---	<1
871	211368_s_at	U13700.1	caspase 1, apoptosis-related cysteine protease (interleukin 1, beta, convertase)	CASP1	<1
872	227811_at	AK000004.1	FGD1 family, member 3	FGD3	>1
873	204116_at	NM_000206.1	interleukin 2 receptor, gamma (severe combined immunodeficiency)	IL2RG	<1
874	212120_at	BF348067	ras-like protein TC10	TC10	<1
875	37986_at	M60459	erythropoietin receptor	EPOR	<1
876	242692_at	AI798758	EST	---	>1
877	209644_x_at	U38945.1	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	CDKN2A	>1

878	228545_at	AI016784	EST	---	<1
879	201858_s_at	J03223.1	proteoglycan 1, secretory granule	PRG1	<1
880	215823_x_at	U64661	EST, Highly similar to PAB1_HUMAN Polyadenylate-binding protein 1 (Poly(A)-binding protein 1) (PABP 1) (PABP1) [H.sapiens]	---	>1
881	201972_at	AF113129.1	ATPase, H+ transporting, lysosomal 70kDa, V1 subunit A, isoform 1	ATP6V1A1	<1
882	201951_at	NM_001627.1	activated leukocyte cell adhesion molecule	ALCAM	<1
883	201986_at	NM_005121.1	thyroid hormone receptor-associated protein, 240 kDa subunit	TRAP240	<1
884	202393_s_at	NM_005655.1	TGFB inducible early growth response	TIEG	>1
885	212118_at	NM_006510.1	ret finger protein	RFP	<1
886	225910_at	BF514723	hypothetical protein LOC284019	LOC284019	<1
887	218795_at	NM_016361.1	lysophosphatidic acid phosphatase	ACP6	>1
888	204985_s_at	NM_024108.1	hypothetical protein MGC2650	MGC2650	>1
889	217436_x_at	M80469	---	---	<1
890	215690_x_at	AL157437.1	GPAA1P anchor attachment protein 1 homolog (yeast)	GPAA1	>1
891	208683_at	M23254.1	calpain 2, (m/II) large subunit	CAPN2	<1
892	223638_at	AL136890.1	hypothetical protein DKFZp434D177	DKFZp434D177	<1
893	218079_s_at	NM_024835.1	C3HC4-type zinc finger protein	LZK1	<1
894	209250_at	BC000961.2	degenerative spermatocyte homolog, lipid desaturase (Drosophila)	DEGS	<1
895	238724_at	R63824	EST	---	>1
896	212809_at	AA152202	hypothetical protein FLJ14639	FLJ14639	>1
897	222391_at	AL080250	hypothetical protein FLJ10856	FLJ10856	<1
898	209533_s_at	AF145020.1	phospholipase A2-activating protein	PLAA	<1
899	218205_s_at	NM_017572.1	MAP kinase-interacting serine/threonine kinase 2	MKNK2	>1
900	232174_at	AA480392	Homo sapiens clone 24838 mRNA sequence	---	>1

901	201068_s_at	NM_002803.1	proteasome (prosome, macropain) 26S subunit, ATPase, 2	PSMC2	<1
902	218573_at	NM_014061.1	APR-1 protein	MAGEH1	<1
903	216272_x_at	AF209931.1	hypothetical protein FLJ13511	7h3	>1
904	222309_at	AW972292	EST	---	>1
905	226461_at	AA204719	homeo box B9	HOXB9	>1
906	214449_s_at	NM_012249.1	ras-like protein TC10	TC10	<1
907	217880_at	AI203880	cell division cycle 27	CDC27	<1
908	213238_at	AI478147	ATPase, Class V, type 10D	ATP10D	<1
909	228464_at	AI651510	EST, Weakly similar to T12486 hypothetical protein DKFZp566H033.1 - human [H.sapiens]	---	<1
910	203157_s_at	AB020645.1	glutaminase	GLS	<1
911	204547_at	NM_006822.1	RAB40B, member RAS oncogene family	RAB40B	>1
912	203067_at	NM_003477.1	E3-binding protein	PDX1	<1
913	228289_at	AI131537	adenylate cyclase 7	ADCY7	<1
914	217955_at	NM_015367.1	BCL2-like 13 (apoptosis facilitator)	BCL2L13	<1
915	201768_s_at	BC004467.1	enthoprotin	ENTH	<1
916	217832_at	NM_006372.1	NS1-associated protein 1	NSAP1	<1
917	226923_at	AW205790	hypothetical protein FLJ39514	FLJ39514	<1
918	217939_s_at	NM_017657.1	hypothetical protein FLJ20080	FLJ20080	<1
919	244732_at	R06827	Homo sapiens, clone IMAGE:5276307, mRNA	---	>1
920	221718_s_at	M90360.1	A kinase (PRKA) anchor protein 13	AKAP13	>1
921	218970_s_at	NM_015960.1	CGI-32 protein	CGI-32	<1
922	214259_s_at	AW074911	aldo-keto reductase family 7, member A2 (aflatoxin aldehyde reductase)	AKR7A2	>1
923	204020_at	BF739943	purine-rich element binding protein A	PURA	<1
924	205565_s_at	NM_000144.1	Friedreich ataxia	FRDA	<1
925	218768_at	NM_020401.1	nuclear pore complex protein	NUP107	>1
926	202011_at	NM_003257.1	tight junction protein 1 (zona occludens 1)	TJP1	<1

927	211423_s_at	D85181.1	sterol-C5-desaturase (ERG3 delta-5-desaturase homolog, fungal)-like	SC5DL	<1
928	202738_s_at	BG149218	phosphorylase kinase, beta	PHKB	<1
929	228697_at	AW731710	histidine triad nucleotide binding protein 3	HINT3	<1
930	225317_at	AL574669	hypothetical protein MGC2404	MGC2404	>1
931	217368_at	X69909	---	---	>1
932	201393_s_at	NM_000876.1	insulin-like growth factor 2 receptor	IGF2R	<1
933	205158_at	NM_002937.1	ribonuclease, RNase A family, 4	RNASE4	<1
934	200734_s_at	BG341906	ADP-ribosylation factor 3	ARF3	>1
935	239586_at	AA085776	hypothetical protein MGC14128	MGC14128	>1
936	225216_at	AI590719	Homo sapiens cDNA: FLJ21191 fis, clone COL00104.	---	<1
937	203373_at	NM_003877.1	suppressor of cytokine signaling 2	SOCS2	>1
938	218003_s_at	NM_002013.1	FK506 binding protein 3, 25kDa	FKBP3	>1
939	208296_x_at	NM_014350.1	TNF-induced protein	GG2-1	<1
940	217716_s_at	NM_013336.1	protein transport protein SEC61 alpha subunit isoform 1	SEC61A1	<1
941	202028_s_at	BC000603.1	ribosomal protein L38	RPL38	>1
942	218231_at	NM_017567.1	N-acetylglucosamine kinase	NAGK	<1
943	211528_x_at	M90685.1	HLA-G histocompatibility antigen, class I, G	HLA-G	<1
944	203142_s_at	NM_003664.1	adaptor-related protein complex 3, beta 1 subunit	AP3B1	<1
945	230597_at	AI963203	solute carrier family 7 (cationic amino acid transporter, y+ system), member 3	SLC7A3	>1
946	200864_s_at	NM_004663.1	RAB11A, member RAS oncogene family	RAB11A	<1
947	205541_s_at	NM_018094.1	G1 to S phase transition 2	GSPT2	<1
948	209267_s_at	AB040120.1	BCG-induced gene in monocytes, clone 103	BIGM103	<1
949	207428_x_at	NM_001787.1	cell division cycle 2-like 1 (PITSLRE proteins)	CDC2L1	>1
950	205801_s_at	NM_015376.1	guanine nucleotide exchange factor for Rap1	GRP3	<1
951	228614_at	AW182614	hypothetical protein LOC205251	LOC205251	<1
952	230261_at	AA552969	Homo sapiens, clone IMAGE:4816784, mRNA	---	<1

953	229194_at	AL045882	Homo sapiens, clone IMAGE:5273745, mRNA	---	<1
954	224951_at	BE348305	hypothetical protein MGC45411	LOC91012	>1
955	230026_at	N74662	mitochondrial ribosomal protein L43	MRPL43	>1
956	217975_at	NM_016303.1	pp21 homolog	LOC51186	<1
957	212714_at	AL050205.1	c-Mpl binding protein	LOC113251	<1
958	212990_at	AB020717.1	synaptojanin 1	SYNJ1	<1
959	211356_x_at	U66495.1	leptin receptor	LEPR	<1
960	241342_at	BG288115	hypothetical protein BC017881	LOC157378	>1
961	239891_x_at	AA001052	EST, Weakly similar to RB10_HUMAN Ras-related protein Rab-10 [H.sapiens]	---	<1
962	214672_at	AB023215.1	KIAA0998 protein	KIAA0998	>1
963	201628_s_at	NM_006570.1	Ras-related GTP-binding protein	RAGA	<1
964	232761_at	AL117381	cytochrome c oxidase subunit IV isoform 2	COX4I2	>1
965	233164_x_at	AK026955.1	hypothetical protein DKFZp547E052	DKFZp547E052	<1
966	200077_s_at	D87914.1	ornithine decarboxylase antizyme 1	OAZ1	>1
967	219549_s_at	NM_006054.1	reticulon 3	RTN3	<1
968	203560_at	NM_003878.1	gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase)	GGH	>1
969	217923_at	NM_012392.1	PEF protein with a long N-terminal hydrophobic domain (peflin)	PEF	<1
970	201862_s_at	NM_004735.1	leucine rich repeat (in FLII) interacting protein 1	LRRFIP1	<1
971	223400_s_at	AF197569.1	polybromo 1	PB1	<1
972	AFFX-M27830_M_at	M27830	---	---	>1
973	41220_at	AB023208	MLL septin-like fusion	MSF	>1
974	209276_s_at	AF162769.1	glutaredoxin (thioltransferase)	GLRX	<1
975	207627_s_at	NM_005653.1	transcription factor CP2	TFCP2	<1

976	204785_x_at	NM_000874.1	interferon (alpha, beta and omega) receptor 2	IFNAR2	>1
977	222615_s_at	AW206812	hypothetical protein FLJ13902	FLJ13902	>1
978	200949_x_at	NM_001023.1	ribosomal protein S20	RPS20	>1
979	217192_s_at	AL022067	PR domain containing 1, with ZNF domain	PRDM1	>1
980	235792_x_at	AU154663	Homo sapiens mRNA; cDNA DKFZp564L222 (from clone DKFZp564L222)	---	<1
981	213857_s_at	BG230614	Homo sapiens, clone IMAGE:4822825, mRNA	---	<1
982	235507_at	AA461195	similar to hypothetical protein FLJ10883	LOC115294	>1
983	218191_s_at	NM_018368.1	hypothetical protein FLJ11240	FLJ11240	<1
984	200649_at	BC002356.1	nucleobindin 1	NUCB1	<1
985	210260_s_at	BC005352.1	TNF-induced protein	GG2-1	<1
986	209513_s_at	BC004331.1	hypothetical protein MGC10940	MGC10940	<1
987	211801_x_at	AF329637.1	mitofusin 1	MFN1	<1
988	206875_s_at	NM_014720.1	Ste20-related serine/threonine kinase	SLK	<1
989	39705_at	AB014600	SIN3 homolog B, transcriptional regulator (yeast)	SIN3B	<1
990	203658_at	BC001689.1	solute carrier family 25 (carnitine/acylcarnitine translocase), member 20	SLC25A20	<1
991	235566_at	AW591660	Homo sapiens cDNA FLJ39046 fis, clone NT2RP7010612.	---	<1
992	205089_at	NM_003416.1	zinc finger protein 7 (KOX 4, clone HF.16)	ZNF7	>1
993	212040_at	AK025557.1	Homo sapiens, clone IMAGE:6057297, mRNA	---	<1
994	210962_s_at	AB019691.1	A kinase (PRKA) anchor protein (yotiao) 9	AKAP9	<1
995	203053_at	NM_005872.1	breast carcinoma amplified sequence 2	BCAS2	>1
996	233867_at	AK000119.1	EST, Moderately similar to KIAA0737 gene product [Homo sapiens] [H.sapiens]	---	>1
997	200993_at	AL137335.1	EST	---	<1
998	204328_at	NM_007267.2	epidermodysplasia verruciformis 1	EVER1	>1
999	212926_at	AB011166.1	SMC5 structural maintenance of chromosomes 5-like 1 (yeast)	SMC5L1	>1
1000	229353_s_at	AW515443	similar to rat nuclear ubiquitous casein kinase 2	NUCKS	>1

1001	212455_at	N36997	KIAA1966 protein	KIAA1966	<1
1002	202025_x_at	NM_001607.2	acetyl-Coenzyme A acyltransferase 1 (peroxisomal 3-oxoacyl-Coenzyme A thiolase)	ACAA1	>1
1003	235009_at	AI049791	hypothetical protein FLJ33215	FLJ33215	>1
1004	218306_s_at	NM_003922.1	hect (homologous to the E6-AP (UBE3A) carboxyl terminus) domain and RCC1 (CHC1)-like domain (RLD) 1	HERC1	<1
1005	225592_at	D81048	nurim (nuclear envelope membrane protein)	NRM	>1
1006	238604_at	AA768884	Homo sapiens cDNA FLJ25559 fis, clone JTH02834.	---	<1
1007	202264_s_at	NM_006114.1	translocase of outer mitochondrial membrane 40 homolog (yeast)	TOMM40	>1
1008	239258_at	BE551407	EST, Moderately similar to hypothetical protein FLJ20234 [Homo sapiens] [H.sapiens]	---	<1
1009	210538_s_at	U37546.1	baculoviral IAP repeat-containing 3	BIRC3	<1
1010	202545_at	NM_006254.1	protein kinase C, delta	PRKCD	<1
1011	212622_at	D26067.1	KIAA0033 protein	KIAA0033	<1
1012	207431_s_at	NM_003676.1	degenerative spermatocyte homolog, lipid desaturase (Drosophila)	DEGS	<1
1013	218549_s_at	NM_016033.1	CGI-90 protein	CGI-90	>1
1014	225058_at	AL365404.1	G protein-coupled receptor 108	GPR108	<1
1015	224847_at	AW274756	Homo sapiens cDNA FLJ20653 fis, clone KAT01739.	---	<1
1016	222024_s_at	AK022014.1	A kinase (PRKA) anchor protein 13	AKAP13	>1
1017	208882_s_at	U69567	progestin induced protein	DD5	>1
1018	208937_s_at	D13889.1	inhibitor of DNA binding 1, dominant negative helix-loop-helix protein	ID1	>1
1019	200857_s_at	NM_006311.1	nuclear receptor co-repressor 1	NCOR1	<1
1020	219972_s_at	NM_022495.1	chromosome 14 open reading frame 135	C14orf135	>1
1021	226191_at	AW139538	EST, Highly similar to SMD1_HUMAN Small nuclear ribonucleoprotein Sm D1 (snRNP core protein D1) (Sm-D1) (Sm-D autoantigen) [H.sapiens]	---	<1
1022	222129_at	AK026155.1	hypothetical protein MGC3035	MGC3035	<1
1023	201668_x_at	AW163148	myristoylated alanine-rich protein kinase C substrate	MARCKS	>1

1024	208549_x_at	NM_016171.1	prothymosin a14	LOC51685	>1
1025	242241_x_at	R66713	EST	---	>1
1026	211671_s_at	U01351.1	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	NR3C1	<1
1027	221787_at	AF055030.1	PHD zinc finger protein XAP135	XAP135	<1
1028	228600_x_at	BE220330	Homo sapiens mRNA; cDNA DKFZp686F0810 (from clone DKFZp686F0810)	---	<1
1029	213620_s_at	AA126728	intercellular adhesion molecule 2	ICAM2	<1
1030	204267_x_at	NM_004203.1	membrane-associated tyrosine- and threonine-specific cdc2-inhibitory kinase	PKMYT1	>1
1031	205443_at	NM_003082.1	small nuclear RNA activating complex, polypeptide 1, 43kDa	SNAPC1	>1
1032	218408_at	NM_012456.1	translocase of inner mitochondrial membrane 10 homolog (yeast)	TIMM10	>1
1033	221897_at	AA205660	tripartite motif-containing 52	TRIM52	<1
1034	201970_s_at	NM_002482.1	nuclear autoantigenic sperm protein (histone-binding)	NASP	>1
1035	227701_at	AK024739.1	CTCL tumor antigen L14-2	FLJ10188	<1
1036	228549_at	AI491983	EST, Moderately similar to hypothetical protein FLJ20378 [Homo sapiens] [H.sapiens]	---	<1
1037	211404_s_at	BC004371.1	amyloid beta (A4) precursor-like protein 2	APLP2	>1
1038	218905_at	NM_017864.1	hypothetical protein FLJ20530	FLJ20530	>1
1039	203774_at	NM_000254.1	5-methyltetrahydrofolate-homocysteine methyltransferase	MTR	<1
1040	200759_x_at	NM_003204.1	nuclear factor (erythroid-derived 2)-like 1	NFE2L1	<1
1041	242674_at	T82467	Homo sapiens cDNA FLJ41014 fis, clone UTERU2018674.	---	>1
1042	AFFX-HSAC07/X00351_M_at	X00351	actin, beta	ACTB	<1
1043	201025_at	NM_015904.1	translation initiation factor IF2	IF2	<1
1044	226344_at	AI741051	KIAA1789 protein	KIAA1789	<1
1045	227854_at	BE620258	hypothetical protein FLJ10335	FLJ10335	<1

1046	220202_s_at	NM_018835.1	membrane-associated nucleic acid binding protein	MNAB	<1
1047	203158_s_at	AF097493.1	glutaminase	GLS	<1
1048	233186_s_at	AK001039.1	BTG3 associated nuclear protein	BANP	>1
1049	205569_at	NM_014398.1	lysosomal-associated membrane protein 3	LAMP3	<1
1050	222680_s_at	AK001261.1	RA-regulated nuclear matrix-associated protein	RAMP	>1
1051	208523_x_at	NM_003525.1	histone 1, H2bi	HIST1H2BI	>1
1052	207761_s_at	NM_014033.1	DKFZP586A0522 protein	DKFZP586A0522	<1
1053	220547_s_at	NM_019054.1	hypothetical protein MGC5560	MGC5560	<1
1054	224912_at	BE205790	tetratricopeptide repeat domain 7	TTC7	<1
1055	211367_s_at	U13699.1	caspase 1, apoptosis-related cysteine protease (interleukin 1, beta, convertase)	CASP1	<1
1056	209376_x_at	AW084759	splicing factor, arginine/serine-rich 2, interacting protein	SFRS2IP	>1
1057	213932_x_at	AI923492	major histocompatibility complex, class I, A	HLA-A	<1
1058	202261_at	NM_005997.1	transcription factor-like 1	TCFL1	>1
1059	213811_x_at	BG393795	transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47)	TCF3	>1
1060	212833_at	M74089.1	hypothetical protein BC017169	LOC91137	<1
1061	216540_at	X61072.1	T cell receptor alpha locus	TRA@	>1
1062	215284_at	AF070575.1	Homo sapiens clone 24407 mRNA sequence	---	<1
1063	239395_at	AA835887	Homo sapiens, clone IMAGE:5286379, mRNA	---	>1
1064	209388_at	BC000927.1	poly(A) polymerase alpha	PAPOLA	>1
1065	235038_at	BF665176	HIV-1 rev binding protein 2	HRB2	>1
1066	235745_at	AV704183	hypothetical protein FLJ30999	FLJ30999	<1
1067	242048_at	BE905316	EST	---	>1
1068	239250_at	BE966038	hypothetical protein LOC147947	LOC147947	>1

1069	213828_x_at	AA477655	H3 histone, family 3A	H3F3A	>1
1070	222593_s_at	AA584308	hypothetical protein FLJ13117	FLJ13117	>1
1071	229075_at	AI754871	EST	---	<1
1072	219978_s_at	NM_018454.1	nucleolar protein ANKT	ANKT	>1
1073	211676_s_at	AF056979.1	interferon gamma receptor 1	IFNGR1	<1
1074	234347_s_at	AF038554.1	density-regulated protein	DENR	>1
1075	209066_x_at	M26700.1	ubiquinol-cytochrome c reductase binding protein	UQCRB	>1
1076	241435_at	AA702930	EST	---	>1
1077	219507_at	NM_016625.1	hypothetical protein LOC51319	LOC51319	>1
1078	202284_s_at	NM_000389.1	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	CDKN1A	<1
1079	218732_at	NM_016077.1	CGI-147 protein	CGI-147	<1
1080	207654_x_at	NM_001938.1	down-regulator of transcription 1, TBP-binding (negative cofactor 2)	DR1	>1
1081	226671_at	AI150000	Homo sapiens, clone IMAGE:4797120, mRNA	---	<1
1082	227637_at	AV712694	transcription factor CP2	TFCP2	>1
1083	201580_s_at	AL544094	hypothetical protein DJ971N18.2	DJ971N18.2	<1
1084	226580_at	AA779684	breast cancer metastasis-suppressor 1	BRMS1	>1
1085	224312_x_at	BC000675.1	hypothetical protein FLJ20542	FLJ20542	>1
1086	227425_at	AI984607	Homo sapiens cDNA FLJ40165 fis, clone TESTI2015962.	---	<1
1087	202643_s_at	AI738896	tumor necrosis factor, alpha-induced protein 3	TNFAIP3	<1
1088	227080_at	AW003092	Homo sapiens cDNA: FLJ23366 fis, clone HEP15665.	---	>1
1089	235353_at	AI887866	KIAA0746 protein	KIAA0746	>1
1090	209534_x_at	BF222823	A kinase (PRKA) anchor protein 13	AKAP13	>1
1091	235103_at	AA029155	Homo sapiens mRNA; cDNA DKFZp686H1529 (from clone DKFZp686H1529)	---	<1
1092	235474_at	AI241810	EST, Weakly similar to T31613 hypothetical protein Y50E8A.i - Caenorhabditis elegans [C.elegans]	---	<1
1093	218662_s_at	NM_022346.1	chromosome condensation protein G	HCAP-G	>1

1094	208668_x_at	BC003689.1	high-mobility group nucleosomal binding domain 2	HMGN2	>1
1095	214919_s_at	R39094	Homo sapiens, clone IMAGE:3866125, mRNA	---	<1
1096	218976_at	NM_021800.1	J domain containing protein 1	JDP1	<1
1097	241955_at	BE243270	EST, Weakly similar to C34D4.14.p [Caenorhabditis elegans] [C.elegans]	---	>1
1098	201138_s_at	BG532929	Sjogren syndrome antigen B (autoantigen La)	SSB	>1
1099	209056_s_at	AW268817	CDC5 cell division cycle 5-like (S. pombe)	CDC5L	>1
1100	219384_s_at	NM_012091.2	adenosine deaminase, tRNA-specific 1	ADAT1	<1
1101	212886_at	AL080169.1	DKFZP434C171 protein	DKFZP434C171	<1
1102	226773_at	AW290940	Homo sapiens cDNA FLJ35131 fis, clone PLACE6008824.	---	<1
1103	215756_at	AU153979	Homo sapiens cDNA FLJ14231 fis, clone NT2RP3004470.	---	>1
1104	227994_x_at	AA548838	chromosome 20 open reading frame 149	C20orf149	>1
1105	218120_s_at	D21243.1	heme oxygenase (decycling) 2	HMOX2	<1
1106	225092_at	AL550977	rabaptin-5	RAB5EP	<1
1107	220696_at	NM_014129.1	PRO0478 protein	PRO0478	>1
1108	210170_at	BC001017.1	alpha-actinin-2-associated LIM protein	ALP	>1
1109	224648_at	AI860946	vasculin	DKFZp761C169	<1
1110	212830_at	BF110421	EGF-like-domain, multiple 5	EGFL5	<1
1111	213410_at	AL050102.1	DKFZp586F1019 protein	DKFZp586F1019	>1
1112	212718_at	BG110231	poly(A) polymerase alpha	PAPOLA	>1
1113	203173_s_at	AW080196	esophageal cancer associated protein	MGC16824	>1
1114	229520_s_at	BF060678	chromosome 14 open reading frame 118	C14orf118	>1
1115	203974_at	NM_012080.1	family with sequence similarity 16, member A, X-linked	FAM16AX	<1
1116	230075_at	AV724323	RAB39B, member RAS oncogene family	RAB39B	<1
1117	225880_at	BF676081	Homo sapiens cDNA FLJ11174 fis, clone PLACE1007367.	---	<1

1118	222891_s_at	AI912275	B-cell CLL/lymphoma 11A (zinc finger protein)	BCL11A	<1
1119	213494_s_at	AA748649	YY1 transcription factor	YY1	>1
1120	211366_x_at	U13698.1	caspase 1, apoptosis-related cysteine protease (interleukin 1, beta, convertase)	CASP1	<1
1121	221995_s_at	BF195165	mitochondrial ribosomal protein 63	MRP63	>1
1122	203322_at	NM_014913.1	KIAA0863 protein	KIAA0863	<1
1123	243051_at	AW135412	EST	---	>1
1124	207245_at	NM_001077.1	UDP glycosyltransferase 2 family, polypeptide B17	UGT2B17	<1
1125	225651_at	BF431962	hypothetical protein FLJ25157	FLJ25157	<1
1126	232288_at	AK026209.1	Homo sapiens cDNA: FLJ22556 fis, clone HSI01326.	---	<1
1127	218701_at	NM_016027.1	CGI-83 protein	CGI-83	>1
1128	201102_s_at	NM_002626.1	phosphofructokinase, liver	PFKL	>1
1129	210458_s_at	BC003388.1	TRAF family member-associated NFKB activator	TANK	<1
1130	226787_at	BF966015	zinc finger protein 18 (KOX 11)	ZNF18	<1
1131	218679_s_at	NM_016208.1	vacuolar protein sorting 28 (yeast)	VPS28	>1
1132	212232_at	AB023231.1	formin binding protein 4	FNBP4	<1
1133	212221_x_at	AL117536.1	Homo sapiens, clone IMAGE:5278680, mRNA	---	<1
1134	200995_at	AL137335.1	importin 7	IPO7	<1
1135	229549_at	AA868461	calumenin	CALU	<1
1136	227239_at	AV734839	down-regulated by Ctnnb1, a	DRCTNNB1A	<1
1137	210716_s_at	M97501.1	restin (Reed-Steinberg cell-expressed intermediate filament-associated protein)	RSN	<1
1138	235170_at	T52999	hypothetical protein FLJ34299	FLJ34299	>1
1139	216841_s_at	X15132.1	superoxide dismutase 2, mitochondrial	SOD2	>1
1140	204683_at	NM_000873.2	intercellular adhesion molecule 2	ICAM2	<1
1141	228829_at	AI279868	activating transcription factor 7	ATF7	>1
1142	212902_at	BE645231	SEC24 related gene family, member A (S. cerevisiae)	SEC24A	<1
1143	212542_s_at	BF224151	pleckstrin homology domain interacting protein	PHIP	>1

1144	201971_s_at	NM_001690.1	ATPase, H+ transporting, lysosomal 70kDa, V1 subunit A, isoform 1	ATP6V1A1	<1
1145	210266_s_at	AF220137.1	tripartite motif-containing 33	TRIM33	>1
1146	222426_at	BG499947	mitogen-activated protein kinase associated protein 1	MAPKAP1	>1
1147	201840_at	NM_006156.1	neural precursor cell expressed, developmentally down-regulated 8	NEDD8	>1
1148	225282_at	AL137764.1	hypothetical protein AL133206	LOC64744	<1
1149	231931_at	AL355710.1	Homo sapiens EST from clone 112590, full insert	---	>1
1150	202271_at	AB007952.1	KIAA0483 protein	KIAA0483	<1
1151	204215_at	NM_024315.1	hypothetical protein MGC4175	MGC4175	<1
1152	213127_s_at	BG230758	mediator of RNA polymerase II transcription, subunit 8 homolog (yeast)	MED8	<1
1153	217826_s_at	NM_016021.1	ubiquitin-conjugating enzyme E2, J1 (UBC6 homolog, yeast)	UBE2J1	<1
1154	203943_at	NM_004798.1	kinesin family member 3B	KIF3B	<1
1155	209384_at	AA176833	proline synthetase co-transcribed homolog (bacterial)	PROSC	<1
1156	228469_at	BF431902	peptidylprolyl isomerase D (cyclophilin D)	PPID	<1
1157	209093_s_at	K02920.1	glucosidase, beta; acid (includes glucosylceramidase)	GBA	>1
1158	239714_at	AA780063	EST	---	>1
1159	239487_at	AI743261	EST	---	<1
1160	204565_at	NM_018473.1	uncharacterized hypothalamus protein HT012	HT012	<1
1161	201311_s_at	AL515318	SH3 domain binding glutamic acid-rich protein like	SH3BGRL	<1
1162	235606_at	AA417117	Homo sapiens cDNA FLJ31372 fis, clone NB9N42000281.	---	<1
1163	201952_at	NM_001627.1	activated leukocyte cell adhesion molecule	ALCAM	<1
1164	212223_at	AL117536.1	Homo sapiens, clone IMAGE:5278680, mRNA	---	<1
1165	218084_x_at	NM_014164.2	FXYD domain containing ion transport regulator 5	FXYD5	<1
1166	223559_s_at	AF161411.2	HSPC043 protein	HSPC043	<1
1167	208445_s_at	NM_023005.1	bromodomain adjacent to zinc finger domain, 1B	BAZ1B	<1
1168	218423_x_at	NM_016516.1	tumor antigen SLP-8p	HCC8	<1
1169	203320_at	NM_005475.1	lymphocyte adaptor protein	LNK	<1
1170	201618_x_at	NM_003801.2	GPAA1P anchor attachment protein 1 homolog (yeast)	GPAA1	>1

1171	229861_at	N66669	general transcription factor IIH, polypeptide 3, 34kDa	GTF2H3	<1
1172	203420_at	NM_016255.1	family with sequence similarity 8, member A1	FAM8A1	<1
1173	239209_at	AA826931	regenerating islet-derived 1 alpha (pancreatic stone protein, pancreatic thread protein)	REG1A	>1
1174	206874_s_at	AL138761	Ste20-related serine/threonine kinase	SLK	<1
1175	227988_s_at	AW629014	chorea acanthocytosis	CHAC	<1
1176	238346_s_at	AW973003	nuclear receptor coactivator 6 interacting protein	NCOA6IP	>1
1177	203707_at	NM_005741.1	zinc finger protein 263	ZNF263	>1
1178	222790_s_at	BE888593	hypothetical protein FLJ11220	FLJ11220	>1
1179	207734_at	NM_017773.1	hypothetical protein FLJ20340	LAX	<1
1180	201859_at	NM_002727.1	proteoglycan 1, secretory granule	PRG1	<1
1181	216250_s_at	X77598.1	leupaxin	LPXN	<1
1182	217846_at	NM_005051.1	glutaminyl-tRNA synthetase	QARS	>1
1183	202862_at	NM_000137.1	fumarylacetoacetate hydrolase (fumarylacetoacetase)	FAH	<1
1184	209061_at	AF012108.1	similar to glucosamine-6-sulfatases	SULF2	<1
1185	203970_s_at	NM_003630.1	peroxisomal biogenesis factor 3	PEX3	<1
1186	235067_at	D81987	Homo sapiens, clone MGC:27281 IMAGE:4656464, mRNA, complete cds	---	<1
1187	228528_at	AI927692	EST	---	<1
1188	218577_at	NM_017768.1	hypothetical protein FLJ20331	FLJ20331	<1
1189	211089_s_at	Z25434.1	NIMA (never in mitosis gene a)-related kinase 3	NEK3	<1
1190	221778_at	BE217882	KIAA1718 protein	KIAA1718	<1
1191	207981_s_at	NM_001438.1	estrogen-related receptor gamma	ESRRG	<1
1192	219939_s_at	NM_007158.1	NRAS-related gene	D1S155E	>1
1193	201084_s_at	NM_014739.1	Bcl-2-associated transcription factor	BTF	<1
1194	209452_s_at	AF035824.1	vesicle transport through interaction with t-SNAREs homolog 1B (yeast)	VTI1B	>1
1195	214527_s_at	AB041836.1	polyglutamine binding protein 1	PQBP1	<1
1196	222243_s_at	AB051450.1	transducer of ERBB2, 2	TOB2	>1

1197	204192_at	NM_001774.1	CD37 antigen	CD37	<1
1198	217775_s_at	NM_016026.1	retinol dehydrogenase 11 (all-trans and 9-cis)	RDH11	>1
1199	227685_at	AI767750	Homo sapiens cDNA FLJ39046 fis, clone NT2RP7010612.	---	<1
1200	225731_at	AB033049.1	KIAA1223 protein	KIAA1223	<1
1201	209475_at	AF106069.1	ubiquitin specific protease 15	USP15	<1
1202	213024_at	BF593908	TATA element modulatory factor 1	TMF1	<1
1203	221508_at	AF181985.1	STE20-like kinase	JIK	<1
1204	212242_at	AL565074	tubulin, alpha 1 (testis specific)	TUBA1	<1
1205	200607_s_at	BG289967	RAD21 homolog (S. pombe)	RAD21	>1
1206	213671_s_at	AA621558	methionine-tRNA synthetase	MARS	>1
1207	201697_s_at	NM_001379.1	DNA (cytosine-5-)-methyltransferase 1	DNMT1	>1
1208	202105_at	NM_001551.1	immunoglobulin (CD79A) binding protein 1	IGBP1	>1
1209	241370_at	AA278233	Homo sapiens cDNA FLJ37785 fis, clone BRHIP2028330.	---	>1
1210	220368_s_at	NM_017936.1	hypothetical protein FLJ20707	FLJ20707	>1
1211	226710_at	AI199072	ribosomal protein S3A	RPS3A	>1
1212	214317_x_at	BE348997	ribosomal protein S9	RPS9	>1
1213	228341_at	AI809108	Homo sapiens cDNA FLJ36248 fis, clone THYMU2001989.	---	<1
1214	204523_at	NM_003440.1	zinc finger protein 140 (clone pHZ-39)	ZNF140	<1
1215	212465_at	AA524500	hypothetical protein FLJ23027	FLJ23027	>1
1216	203606_at	NM_004553.1	NADH dehydrogenase (ubiquinone) Fe-S protein 6, 13kDa (NADH-coenzyme Q reductase)	NDUFS6	>1
1217	211529_x_at	M90684.1	HLA-G histocompatibility antigen, class I, G	HLA-G	<1
1218	211517_s_at	M96651.1	interleukin 5 receptor, alpha	IL5RA	<1
1219	220946_s_at	NM_014159.1	huntingtin interacting protein B	HYPB	>1
1220	204350_s_at	NM_004270.1	cofactor required for Sp1 transcriptional activation, subunit 9, 33kDa	CRSP9	<1

1221	39582_at	AL050166	Homo sapiens mRNA; cDNA DKFZp586D1122 (from clone DKFZp586D1122)	---	<1
1222	204645_at	NM_001241.1	cyclin T2	CCNT2	<1
1223	211136_s_at	BC004865.1	cleft lip and palate associated transmembrane protein 1	CLPTM1	<1
1224	229312_s_at	BF434321	protein kinase anchoring protein GKAP42	GKAP42	>1
1225	226504_at	AA522720	Homo sapiens, similar to CG12393 gene product, clone IMAGE:5188623, mRNA, partial cds	---	>1
1226	221547_at	BC000794.1	PRP18 pre-mRNA processing factor 18 homolog (yeast)	PRPF18	<1
1227	238035_at	N66313	EST	---	<1
1228	213011_s_at	BF116254	triosephosphate isomerase 1	TPI1	>1
1229	208718_at	Z97056	Homo sapiens, clone IMAGE:5264473, mRNA	---	<1
1230	204686_at	NM_005544.1	insulin receptor substrate 1	IRS1	>1
1231	225763_at	AI659418	hypothetical protein MGC21854	MGC21854	<1
1232	212643_at	AI671747	chromosome 14 open reading frame 32	C14orf32	>1
1233	203060_s_at	AF074331.1	3'-phosphoadenosine 5'-phosphosulfate synthase 2	PAPSS2	<1
1234	206900_x_at	NM_021047.1	zinc finger protein 253	ZNF253	<1
1235	225798_at	AI990891	hypothetical protein DKFZp761K2222	DKFZp761K2222	<1
1236	209619_at	K01144.1	CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated)	CD74	<1
1237	200996_at	NM_005721.2	ARP3 actin-related protein 3 homolog (yeast)	ACTR3	<1
1238	228150_at	AI807478	regucalcin gene promotor region related protein	RGPR	<1
1239	218152_at	NM_018200.1	high-mobility group 20A	HMG20A	>1
1240	202546_at	NM_003761.1	vesicle-associated membrane protein 8 (endobrevin)	VAMP8	<1
1241	218603_at	NM_016217.1	hHDC for homolog of Drosophila headcase	HDCL	<1
1242	213793_s_at	BE550452	homer homolog 1 (Drosophila)	HOMER1	>1
1243	205917_at	NM_003417.1	---	---	<1

1244	218669_at	NM_021183.1	hypothetical protein similar to small G proteins, especially RAP-2A	LOC57826	<1
1245	226381_at	AW450329	hypothetical protein FLJ20366	FLJ20366	<1
1246	211065_x_at	BC006422.1	phosphofructokinase, liver	PFKL	>1
1247	224848_at	AW274756	Homo sapiens cDNA FLJ20653 fis, clone KAT01739.	---	<1
1248	212616_at	AB002306.1	hypothetical protein MGC17528	MGC17528	<1
1249	232171_x_at	AK001742.1	hypothetical protein DKFZp434G0522	DKFZp434G0522	>1
1250	237181_at	AI478850	EST	---	>1
1251	204171_at	NM_003161.1	ribosomal protein S6 kinase, 70kDa, polypeptide 1	RPS6KB1	<1
1252	201780_s_at	NM_007282.1	ring finger protein 13	RNF13	<1
1253	215148_s_at	AI141541	amyloid beta (A4) precursor protein-binding, family A, member 3 (X11-like 2)	APBA3	<1
1254	203359_s_at	AL525412	c-myc binding protein	MYCBP	<1
1255	201788_at	NM_007372.1	RNA helicase-related protein	RNAHP	<1
1256	235661_at	T99553	EST	---	<1
1257	202375_at	NM_014822.1	SEC24 related gene family, member D (S. cerevisiae)	SEC24D	<1
1258	203491_s_at	AI123527	KIAA0092 gene product	KIAA0092	>1
1259	221989_at	AW057781	ribosomal protein L10	RPL10	<1
1260	65630_at	AI742455	SIPL protein	SIPL	<1
1261	214030_at	BE501352	hypothetical protein DKFZp667G2110	DKFZp667G2110	<1
1262	243552_at	AW008914	EST	---	>1
1263	214615_at	NM_014499.1	purinergic receptor P2Y, G-protein coupled, 10	P2RY10	<1
1264	203404_at	NM_014782.1	armadillo repeat protein ALEX2	ALEX2	<1
1265	212877_at	AA284075	kinesin 2 60/70kDa	KNS2	>1
1266	231059_x_at	AI744643	SCAN domain containing 1	SCAND1	>1

1267	225681_at	AA584310	collagen triple helix repeat containing 1	CTHRC1	>1
1268	227946_at	AI955239	oxysterol binding protein-like 7	OSBPL7	>1
1269	221323_at	NM_025218.1	UL16 binding protein 1	ULBP1	>1
1270	232431_at	AI934556	Human glucocorticoid receptor alpha mRNA, variant 3' UTR	---	<1
1271	32209_at	AF052151	Mouse Mammary Turmor Virus Receptor homolog 1	MTVR1	<1
1272	201980_s_at	NM_012425.2	Ras suppressor protein 1	RSU1	<1
1273	201558_at	NM_003610.1	RAE1 RNA export 1 homolog (S. pombe)	RAE1	>1
1274	221613_s_at	AL136598.1	protein associated with PRK1	AWP1	<1
1275	243570_at	AA921960	EST, Moderately similar to T12486 hypothetical protein DKFZp566H033.1 - human [H.sapiens]	---	<1
1276	214179_s_at	H93013	nuclear factor (erythroid-derived 2)-like 1	NFE2L1	<1
1277	224768_at	AW451291	hypothetical protein FLJ10006	FLJ10006	<1
1278	227518_at	AW051365	EST, Moderately similar to hypothetical protein FLJ20378 [Homo sapiens] [H.sapiens]	---	<1
1279	218850_s_at	NM_014240.1	LIM domains containing 1	LIMD1	>1
1280	201408_at	AI186712	protein phosphatase 1, catalytic subunit, beta isoform	PPP1CB	<1
1281	214097_at	AW024383	ribosomal protein S21	RPS21	>1
1282	242208_at	AI634543	EST, Weakly similar to hypothetical protein FLJ20489 [Homo sapiens] [H.sapiens]	---	<1

[00234] Still further, Table 3 sets forth markers which are significantly expressed in myeloma samples from non-responder patients whose disease is refractory (i.e. progressive disease) to treatment with bortezomib. The markers identified in Table 3 were identified similar to the methods described above for Table 1. These markers will serve to distinguish refractory patients from those who will be either stable or responsive to treatment.

TABLE 3 Predictive Markers in Progressive Disease

No.	Probeset _ID	RefSeq/ Genbank Accession	Title	Gene Symbol	Unigene
1283	205124_ at	NM_005919. 1	MADS box transcription enhancer factor 2, polypeptide B (myocyte enhancer factor 2B)	MEF2B	Hs.78881
1284	206626_ x_at	BC001003.2	synovial sarcoma, X breakpoint 1	SSX1	Hs.194759
34	224918_ x_at	AI220117	microsomal glutathione S-transferase 1	MGST1	Hs.355733
1285	206640_ x_at	NM_001477. 1	G antigen 7B	GAGE7 B	Hs.251677
223	227174_ at	Z98443			Hs.86366
1286	227617_ at	BF315093	Weakly similar to MUC2_HUMAN Mucin 2 precursor		Hs.22293
1287	207086_ x_at	NM_001474. 1	G antigen 4	GAGE4	Hs.183199
1288	209732_ at	BC005254.1	Similar to C-type (calcium dependent, carbohydrate-recognition domain) lectin, superfamily member 2 (activation-induced)	CLECS F2	Hs.85201
1289	214596_ at	T15991	cholinergic receptor, muscarinic 3	CHRM3	Hs.7138
1290	202779_s _at	NM_014501. 1	ubiquitin carrier protein (E2-EPF)	E2-EPF	Hs.174070
1291	231568_ at	AI200804	similar to Proliferation-associated protein 2G4 (Cell cycle protein p38-2G4 homolog)		Hs.98612
1292	207480_s _at	NM_020149. 1	TALE homeobox protein Meis2e	MEIS2	Hs.283312
1293	230352_ at	AI392908	phosphoribosyl pyrophosphate synthetase 2	PRPS2	Hs.2910
1294	202411_ at	NM_005532. 1	interferon, alpha-inducible protein 27	IFI27	Hs.278613
17	215733_ x_at	AJ012833.1	CTL-recognized antigen on melanoma (CAMEL)	CTAG2	Hs.87225
1295	243030_ at	AA211369			Hs.269493

18	210546_x_at	U87459.1	autoimmunogenic cancertestis antigen NY-ESO-1	CTAG1	Hs.167379
1296	202044_at	AU159484	glucocorticoid receptor DNA binding factor 1	GRLF1	Hs.102548
1297	217977_at	NM_016332.1	selenoprotein X, 1	SEPX1	Hs.279623
1298	231000_at	BE350315	receptor tyrosine kinase-like orphan receptor 2	ROR2	Hs.155585
1299	238587_at	AI927919	Nm23-phosphorylated unknown substrate		Hs.187625
1300	239119_at	AW014374			Hs.144849
1301	236741_at	AW299463			Hs.208067
223	227174_at	Z98443			Hs.86366
1302	206897_at	NM_003785.2	G antigen, family B, 1 (prostate associated)	GAGEB1	Hs.128231
205	204836_at	NM_000170.1	glycine dehydrogenase (decarboxylating; glycine decarboxylase, glycine cleavage system protein P)	GLDC	Hs.27
1303	208282_x_at	NM_020363.1	deleted in azoospermia 2	DAZ2	Hs.283813
1304	216922_x_at	AF271088.1	deleted in azoospermia	DAZ	Hs.70936
1305	231771_at	AI694073	gap junction protein, beta 6 (connexin 30)	GJB6	Hs.48956
267	231131_at	AA909330	weakly similar to GAR2 PROTEIN		Hs.112765
1306	217007_s_at	AK000667.1	a disintegrin and metalloproteinase domain 15 (metargidin)		Hs.92208
1307	220445_s_at	NM_004909.1	taxol resistance associated gene 3	TRAG3	Hs.251377
1308	233216_at	AV741116			Hs.283933
1309	211323_s_at	L38019.1	inositol 1,4,5-trisphosphate receptor type 1	ITPR1	Hs.198443
1310	224188_s_at	BC001208.1	Similar to hypothetical protein LOC63929		Hs.182061
1311	213222_at	KIAA0581	1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase beta 1	PLCB1	Hs.41143
1312	201897_s_at	AF274941.1	CDC28 protein kinase 1	CKS1	Hs.77550
1313	206012_at	NM_003240.1	endometrial bleeding associated factor (left-right determination, factor A; transforming growth factor beta superfamily)	LEFTB	Hs.25195

Classifiers

[00235] Various algorithms are currently available that can be used to classify patient samples into prior defined groups using a given set of features. Therefore, the combination of markers selected through the feature selection process may be used in one of the following classifying algorithms in order to derive a prediction equation as to whether the patient sample is sensitive or resistant. The classifiers used in the present invention were: 1) Weighted Voting ("WV"); and 2) Combination of Thresholded Features ("CTF").

[00236] The Weighted Voting classifier was implemented as described by Golub et al., "Molecular Classification of Cancer: Class discovery and class prediction by marker expression monitoring." Science, 286:531-537 (1999), the contents of which are incorporated herein by reference. For weighted voting, the classification criterion for each feature used the following formula for the weighted vote of feature *j*:

$$V_j = \frac{(\bar{x}_R - \bar{x}_S)}{S_S + S_R}\left[z_j - \left(\frac{\bar{x}_R + \bar{x}_S}{2} \right)_j \right]$$

where z_j represents the log expression value for the j^{th} feature in the set. For the class indicated by the subscript, $\bar{x}$ represents the mean log expression value of the *j*th feature, and *S* represents the standard deviation. The first term on the right hand side of the equation is signal-to-noise ratio (the weight given to this feature in the weighted voting), while the subtracted term is called the decision boundary. To determine the class prediction, the weighted votes for all the features in the set are summed. If the result is greater than 0, then the prediction is class *R*; otherwise, the prediction is class *S*. For each prediction, a confidence is also computed. To compute the confidence, each feature in the set is labeled as being in agreement or disagreement with the class prediction. Let v_a be the sum of the absolute values of the votes of the features in agreement with the class prediction, and let v_d be the sum of absolute values of the votes in disagreement with the class prediction. Then the prediction confidence is defined as:

$$C = \frac{v_a}{v_a + v_d}$$

[00237] The CTF classifier first chooses a threshold on the normalized expression value for each feature. The CTF threshold is the CBT threshold divided by the CBT feature filtering score, each of which are described above. Expression values are then divided by this threshold, resulting in a "threshold-normalized expression value." The threshold-normalized expression values of the features in the marker set or model are then combined

into a "combined value" using one of these methods: (1) average, (2) maximum. In preferred embodiments, the first approach, average, is used. Finally, a threshold on the combined value is determined as the average value of the combined values in class A, plus some number of standard deviations of the combined values in class A. In preferred embodiments, the number of standard deviations is 2. Using the terminology introduced in the description of the CBT feature filtering method, samples with a combined value below this threshold are classified into class *A*, and samples with a combined value above this threshold are classified into class *B*.

Feature Selection

[00238] Feature selection is the process of determining the best subset of the 44,928 available features in the dataset, resulting in a combination of features, that form a marker set or model, to classify patients into sensitive and resistant groups. The first step is filtering to the top 100 markers, as described above. Next, for building Weighted Voting (WV) marker sets, a standard feature selection method, sequential forward feature selection, is used (Dash and Liu, "Feature Selection for Classification," Intelligent Data Analysis 1:131-156, 1997). For building CTF marker sets, two methods were utilized: selection of the top N CBT scored markers (N<=100), and exhaustive search of all one- and two-feature models. We now describe how each of these is applied to our dataset to select features.

[00239] For the WV models, the top 100 SNR markers were determined. Sequential forward selection starts with no markers in the set.

[00240] At each iteration, a new feature set is formed by adding a feature selected by an evaluation function. Iteration terminates when no feature can be added that improves the evaluation function. The evaluation function has two parts. The first part is the number of samples correctly predicted either (1) by the model built on all of the samples, or (2) in leave-one-out cross-validation (Dash and Liu, 1997). Ties in the first part of the evaluation function are broken by a value equal to the sum of the confidences of the correct predictions less the sum of the confidences of the incorrect predictions. This second part of the evaluation function favors sets that have higher confidence and more correct predictions.

[00241] Each probe set was used as a single-marker model to predict bortezomib response. Multiple marker sets were generated by repeated rounds of feature selection, each time removing the features already selected. The score of each model was determined. The probe set comprising the highest-scoring model was selected.

[00242] The remaining probe sets were each used one at a time in a model along with the already-selected probe set(s). Each of these models was given a score. If the score of the new model was no higher than the score of the already-selected markers, then marker selection stopped, and the algorithm goes on to final selection by setting aside and continuing with selection of additional set(s) (see below). Otherwise, the probe set that was added to the already-selected markers to obtain the model with the highest score was added to the list of selected markers, and the algorithm returns to selection of additional markers to improve the score.

[00243] Upon final selection where no additional marker improves the score, the selected markers are set aside. Marker selection is then initiated as described above. This process is repeated until there are 5 sets of selected markers. These are combined into one complete predictive marker set.

[00244] For building CTF marker sets, the top 100 CBT features are considered for use in sets, and all one- and two-feature sets are evaluated exhaustively. The score for a given set is the number of class B samples which are above the CTF threshold (described above) for that set. Ties between CTF marker sets are broken by the best CBT score (described above) of any of the constituent markers in a set.

[00245] An example of a weighted voting predictive marker set identified using the WV and SNR scored markers is set forth in Table 4. This procedure is one of many described herein as well as others known in the art, which can be used to identify and select markers for sets predicting proteasome inhibition response in cancer patients. This procedure is the same as the procedure used in cross-validation to determine the predictive accuracy of the method (see Classification Accuracy below:

TABLE 4: Weighted Voting Predictive Marker Set

No.	Decision boundary	Weight	Probe set ID	Title	Gene Symbol
143	0.5177	0.8165	200965_s_at	actin binding LIM protein 1	ABLIM1
141	0.3222	0.9174	234428_at	Homo sapiens mRNA; cDNA DKFZp564I1316 (from clone DKFZp564I1316)	---
221	1.1666	-0.8281	223996_s_at	mitochondrial ribosomal protein L30	MRPL30
94	0.9622	-0.8998	222555_s_at	mitochondrial ribosomal protein L44	MRPL44
147	0.29	0.9019	220572_at	hypothetical protein DKFZp547G183	DKFZp547G183
242	0.8798	-0.739	225647_s_at	cathepsin C	CTSC
180	0.3451	0.8046	227692_at	guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 1	GNAI1
279	0.8811	0.7428	221223_x_at	cytokine inducible SH2-containing protein	CISH
163	0.4398	0.8189	204287_at	synaptogyrin 1	SYNGR1
38	0.4805	0.8322	216835_s_at	docking protein 1, 62kDa (downstream of tyrosine kinase 1)	DOK1
277	1.0222	-0.7718	222713_s_at	Fanconi anemia, complementation group F	FANCF
138	0.3196	0.9477	212109_at	HN1 like	HN1L
36	0.4335	0.897	239476_at	Homo sapiens cDNA FLJ36491 fis, clone THYMU2018197.	---
154	0.5779	-0.8579	218438_s_at	endothelial-derived gene 1	EG1
83	0.9308	-0.9007	201575_at	SKI-interacting protein	SNW1
137	2.121	-0.9414	200043_at	enhancer of rudimentary homolog (Drosophila)	ERH
165	0.8934	-0.8614	210250_x_at	adenylosuccinate lyase	ADSL
251	1.5602	-0.7928	208642_s_at	X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining; Ku autoantigen, 80kDa)	XRCC5
120	0.3485	0.8612	217687_at	adenylate cyclase 2 (brain)	ADCY2
152	1.3737	-0.8783	201682_at	peptidase (mitochondrial processing) beta	PMPCB
96	1.2482	-0.8447	222530_s_at	McKusick-Kaufman syndrome	MKKS
245	0.3578	0.7543	203561_at	Fc fragment of IgG, low affinity IIa, receptor for (CD32)	FCGR2A
241	0.9737	-0.8018	222893_s_at	hypothetical protein FLJ13150	FLJ13150
260	1.5048	-0.792	222531_s_at	chromosome 14 open reading frame 108	C14orf108

311	2.3688	-0.7505	200826_at	small nuclear ribonucleoprotein D2 polypeptide 16.5kDa	SNRPD2
213	0.3054	-0.834	226882_x_at	WD repeat domain 4	WDR4
224	1.2833	0.7725	235875_at	ESTs	---
290	0.8235	-0.7645	218139_s_at	chromosome 14 open reading frame 108	C14orf108
145	1.6774	-0.9194	232075_at	recombination protein REC14	REC14
312	2.2771	-0.7446	203663_s_at	cytochrome c oxidase subunit Va	COX5A
49	1.0533	-0.7456	208743_s_at	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide	YWHAB
160	1.1116	-0.8655	202567_at	small nuclear ribonucleoprotein D3 polypeptide 18kDa	SNRPD3
289	0.577	0.7398	208844_at	---	---
87	0.7265	0.7845	234021_at	Homo sapiens cDNA: FLJ21331 fis, clone COL02520.	---
170	0.4024	0.8105	216287_at	---	---
129	2.216	-0.8395	200814_at	proteasome (prosome, macropain) activator subunit 1 (PA28 alpha)	PSME1
149	0.7958	0.8846	221569_at	hypothetical protein FLJ20069	FLJ20069
243	0.7858	0.7564	233876_at	Homo sapiens cDNA FLJ20670 fis, clone KAIA4743.	---
195	1.1291	0.7902	58367_s_at	hypothetical protein FLJ23233	FLJ23233
190	0.7554	0.7919	205807_s_at	tuftelin 1	TUFT1

Classification Accuracy

[00246] To determine the ability of the selected model to predict sensitivity or resistance in an independent group of tumors, five-fold cross-validation was applied. For more information on cross-validation, see for example Kohavi and John, "Wrappers for Feature Subset Selection," Artificial Intelligence 97 (1-2) (1997) pp. 273-324. Cross-validation provides for repeated division of the data set into training and test sets, building the model each time using only the training set, then evaluating its accuracy on the withheld test set. Five-fold cross-validation means that the training set contains 80% and the test set 20% of the original data set. The filtering, feature selection and model building operations are performed only on the training set, and the resulting models are then applied to the test set. Classification accuracy is measured only on the test sets, across multiple runs of cross-validation.

[00247] To determine if the most highly predictive models could be obtained by chance alone, a permutation test was performed. The labels were permuted on the 44 discovery samples 10 times; the entire marker selection procedure was repeated. Using Weighted Voting on the responders vs others comparison, for example, the overall error rate for the permuted models was 50%, compared to 29% for the observed labels. These results suggest that it is unlikely that those models could be identified by chance alone. In the refractory vs others comparisons, we did not see clear improvement of prediction accuracy when compared to permuted sample labels. However, we report here individual markers that have relatively high single-marker SNR or CBT scores.

[00248] It will be appreciated that additional marker sets may thus be obtained by employing the methods described herein for identifying models. There are many highly correlated features that could be substituted for each other in the models; these are not all listed.

Specific Application of Class Prediction

Weighted Voting (WV)

[00249] Here we illustrate how to apply a Weighted Voting model to obtain a prediction of Response or Non-response for a given patient, using the algorithm described herein. Using the 44 patients classified into Responsive or Nonresponsive groups, the table below shows the SNR scores and decision boundaries for each of the markers in a Weighted Voting predictive set built from the data set. Also indicated is whether the marker is more highly expressed in Responsive (R) or in Non-responsive (NR) patients. For one illustrative Non-responsive patient in the data set, the votes contributed by each marker are shown in Table 5. The sum of the vote weights is less than 0, indicating a prediction of Non-responsive. The confidence in the predicted class (Non-responsive) is 0.8431.

TABLE 5 Weighted Voting Predictive Marker Set

No.	Probe Set ID	Gene Symbol	SNR scores	Decision boundary	Ex. patient log expression	Vote weight	Vote	Confidence
143	200965_s_at	ABLIM1	0.8165	0.5177	0.3085	-0.1708	NR	
141	234428_at	---	0.9174	0.3222	0.201	-0.1112	NR	
221	223996_s_at	MRPL30	-0.8281	1.1666	1.0436	0.1019	R	
94	222555_s_at	MRPL44	-0.8998	0.9622	1.2401	-0.2501	NR	
147	220572_at	DKFZp547G183	0.9019	0.29	0.2731	-0.0153	NR	
	Total					-0.4454	NR	0.8431

[00250] It will be appreciated that similar methods may be employed utilizing the marker sets of the present invention.

Combination of Threshold Features (CTF)

[00251] Using the 44 patients classified into Responsive or Nonresponsive groups, the normalization threshold for each of the up-in-Nonpredictive markers in a CTF predictive set was built from our data set. Each marker value for a patient expression is scaled by dividing by a factor which is the mean of the Responsive class divided by the CBT score for that marker. Normalized expression values are summed to determine the combined predictive value for that patient. The threshold above which patients are predicted to be Nonresponsive was determined to be 59.15, by the CTF method described above. Because the average scaled expression value for this patient is 46.81, which is less than 59.15, the patient is predicted to be responsive. See Table 6.

[00252] It will be appreciated that similar methods may be employed utilizing one or more markers from the identified marker sets of the present invention in order to generate similar Predictive Marker Sets.

TABLE 6 CTF Predictive Marker Set

No.	Probeset ID	RefSeq/ Genbank Accession	Title	Gene Symbol	Normalization factor	gene expr.	Normalized gene expression
28	201457_x_at	AF081496.1	BUB3 budding uninhibited by benzimidazoles 3 homolog (yeast)	BUB3	250.785036	549.1	2.18952458
152	201682_at	NM_004279.1	peptidase (mitochondrial processing) beta	PMPCB	181.94166	373	2.05010771
178	206978_at	NM_000647.2	chemokine (C-C motif) receptor 2	CCR2	248.903364	263	1.05663498
5	214265_at	AI193623	integrin, alpha 8	ITGA8	141.445138	176.5	1.24783363
197	217466_x_at	L48784	---	---	197.537832	833.4	4.21893868
158	217915_s_at	NM_016304.1	chromosome 15 open reading frame 15	C15orf15	218.690016	629.7	2.87941814
16	217969_at	NM_013265.2	melanoma antigen, family D, 1	MAGED1	206.919392	426.4	2.06070584
146	220565_at	NM_016602.1	G protein-coupled receptor 2	GPR2	70.449873	53.1	0.75372741
150	222427_s_at	AK021413.1	leucyl-tRNA synthetase	LARS	247.606604	721.1	2.91228097
207	222465_at	AF165521.1	chromosome 15 open reading frame 15	C15orf15	404.384832	1167.7	2.88759594
144	222783_s_at	NM_022137.1	SPARC related modular calcium binding 1	SMOC1	103.896695	119.9	1.15403093
167	223358_s_at	AW269834	Homo sapiens cDNA FLJ33024 fis, clone THYMU1000532.	---	131.346515	296.2	2.25510361
84	224985_at	BE964484	Homo sapiens, clone IMAGE:3446533, mRNA	---	304.941586	860.4	2.82152399
162	225065_x_at	AI826279	hypothetical protein MGC40157	MGC40157	386.788155	943.5	2.43931979
199	225698_at	BF314746	TIGA1	TIGA1	285.001406	1317.3	4.62208246
188	226392_at	AI888503	Homo sapiens cDNA: FLJ21652 fis, clone COL08582.	---	249.877029	421.8	1.68803032
171	228332_s_at	AA526939	selenoprotein H	SELH	869.698724	1647.4	1.89421918
177	231045_x_at	H29876	selenoprotein H	SELH	620.98954	1078.1	1.7361001
145	232075_at	BF791874	recombination protein REC14	REC14	179.443992	540.9	3.01431101
140	232231_at	AL353944.1	Runt domain transcription factor 2	RUNX2	32.563013	95.4	2.92970432
				sum of normalized expression values			46.8111936
				threshold of control values			59.15
			(> threshold = nonresponder; <threshold = responder)	Responder or nonresponder?			Responder

Biological Annotation of Predictive markers

Among the response genes identified in Table 1 and Table 2, are a subset of genes whose putative biological function or functions are particularly interesting, including function(s) particularly relevant to the use of proteasome inhibitors for the treatment of cancers, including myeloma. Some of the genes are known to be involved in the initiation or progression of myeloma, the growth, survival or signaling of lymphoid cells, the regulation of drug metabolism or apoptotic pathways or encode components of the ubiquitin/proteasome pathway that is directly targeted by proteasome inhibitors. For example, this analysis identified genes in Table 1 that are associated with cellular adhesion (No. 1 to 5), apoptotic signalling (6 to 13), cancer antigen (14 to 27), cell cycle(28 to 33), drug metabolism(34 to 35), drug resistance(36 to 37), growth control, hematopoesis(38 to 44), mitogenic signaling (45-53), myeloma signaling(53 to 61), myeloma translocation(62-73), NFkB pathway(74-77), oncogenes(78 to 82) , oncogenic signaling(83 to 93), protein homeostasis(94 to 118), tumor suppressor pathway(119 to 128), and the ubiquitin/proteasome pathway(129 to 136). Additionally, the genes identified in this exercise also correspond to genes also correspond to the predictive markers associated with progressive disease in Table 2. See Table 7.

[00253] The identification of such genes strengthens the hypothesis that the genes identified with these methodologies are indeed related to cancer biology and the potential sensitivity of a hematological tumor to the anti-cancer actions of a proteasome inhibitor (e.g., bortezomib). Further, the description of such functional molecules as markers of response could facilitate selection of the most appropriate markers for inclusion in a diagnostic tool. In cases where 2 distinct probesets provide equal predictive information, the inclusion of these or other markers known to be biologically relevant could facilitate uptake and implementation of the diagnostic method. Finally, characterization of these functional molecules and pathways may enable the identification of new and possibly improved markers that act in the same or similar biological pathways.

[00254] Further, this analysis indicates additional genomic markers of response may be found in these biological pathways. For example, the "oncogenic signaling" category contains several components of the Wnt signaling pathway. Thus, other genes or proteins that function in the Wnt pathway that may also be employed as response markers.Additional markers in these identified pathways may also function alone or in conjunction with markers shown in Table 1 and Table 2 to effectively predict response to treatment with bortezomib.

TABLE 7: Biological Annotation

No.	Probes et ID	Title	Gene Symbol	R / NR	supplemental annotation	Biological Category
1	204298 _s_at	lysyl oxidase	LOX	R	lysyl oxidase may play an important role in metastasis of colon, espohageal, cardiac, and gastric carcinomas	Adhesion
2	205884 _at	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	ITGA4	NR	Alpha 4 combines with beta 1 (ITGB1) on T-cells to form the integrin very late (activation) antigen 4 ('VLA-4') that can bind to the extracellular matrix molecules fibronectin or thrombospondin, and is also a ligand for the cell surface molecule vascular cell adhesion molecule 1 ('VCAM-1'). In addition, alpha 4 combines with beta 7 to form the lymphocyte homing receptor known as 'LPAM-1' (lymphocyte Peyer Patch adhesion molecule 1). Integrins are also known to participate in cell-surface mediated signalling.	Adhesion
3	228841 _at	Homo sapiens cDNA FLJ32429 fis, clone SKMUS2001014.	---	NR	An inhibitor of matrix metalloproteinases. Prohibit the degradation of the extracellualr matrix which is often a key step in the metastasis of tumor cells	Adhesion
4	243366 _s_at	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	ITGA4	NR	Alpha 4 combines with beta 1 (ITGB1) on T-cells to form the integrin very late (activation) antigen 4 ('VLA-4') that can bind to the extracellular matrix molecules fibronectin or thrombospondin, and is also a ligand for the cell surface molecule vascular cell adhesion molecule 1 ('VCAM-1'). In addition, alpha 4 combines with beta 7 to form the lymphocyte homing receptor known as 'LPAM-1' (lymphocyte Peyer Patch adhesion molecule 1). Integrins are also known to participate in cell-surface mediated signalling.	Adhesion
5	214265 _at	integrin, alpha 8	ITGA8	NR		Adhesion
6	203949 _at	myeloperoxidase	MPO	R	MPO derived oxidants are involved in caspase-3 activation and apoptosis, also translocations invoving this gene are often found in	Apoptotic signalling

7	207341_at	proteinase 3 (serine proteinase, neutrophil, Wegener granulomatosis autoantigen)	PRTN3	R	Cleavage of p21waf1 by proteinase-3, a myeloid-specific serine protease, potentiates cell proliferation. Also proteinase-3 mediates doxorubicin-induced apoptosis in the HL-60 leukemia cell line, and is downregulated in its doxorubicin-resistant variant	Apoptotic signalling
8	203948_s_at	myeloperoxidase	MPO	R	MPO derived oxidants are involved in caspase-3 activation and apoptosis, also translocations invoving this gene are often found in leukemia	Apoptotic signalling
9	224461_s_at	apoptosis-inducing factor (AIF)-homologous mitochondrion-associated inducer of death	AMID	NR	Overexpression of this gene has been shown to induce apoptosis. The expression of this gene is found to be induced by tumor suppressor protein p53 in colon caner cells.	Apoptotic signalling
10	206056_x_at	sialophorin (gpL115, leukosialin, CD43)	SPN	R	engagement of CD43 may, presumably through the repressing transcription, initiate a Bad-dependent apoptotic pathway.	Apoptotic signalling
11	203489_at	CD27-binding (Siva) protein	SIVA	NR	This protein seems to have an important role in the apoptotic (programmed cell death) pathway induced by the CD27 antigen, a member of the tumor necrosis factor receptor (TFNR) superfamily, and it also binds to the CD27 antigen cytoplasmic tail.	Apoptotic signalling
12	226507_at	p21/Cdc42/Rac1-activated kinase 1 (STE20 homolog, yeast)	PAK1	NR	(Pak1, Pak2, Pak3) have been studied in greater detail and shown to be involved in the regulation of cellular processes such as gene transcription, cell morphology, motility, and apoptosis.	Apoptotic signalling

13	216055_at	platelet-derived growth factor beta polypeptide (simian sarcoma viral (v-sis) oncogene homolog)	PDGFB	R	Most proliferating cells are programmed to undergo apoptosis unless specific survival signals are provided. Platelet-derived growth factor promotes cellular proliferation and inhibits apoptosis. Romashkova and Makarov (1999) showed that PDGF activates the RAS/PIK3/AKT1/IKK/NFKB1 pathway. In this pathway, NFKB1 (164011) does not induce c-myc and apoptosis, but instead induces putative antiapoptotic genes. In response to PDGF, AKT1 (164730) transiently associates with IKK (see 600664) and induces IKK activation. The authors suggested that under certain conditions PIK3 (see 171834) may activate NFKB1 without the involvement of NFKBIA (164008) or NFKBIB (604495) degradation.	Apoptotic signalling
14	209942_x_at	melanoma antigen, family A, 3	MAGEA 3	NR	A cancer antigen that binds to pro-caspase 12 and prevents its cleavage, therby preventing apoptosis reulting from ER stress , including the unfolded protein response	Cancer Antigen
15	214612_x_at	Human MAGE-6 antigen (MAGE6) gene	---	NR	A cancer/testis antigen	Cancer Antigen
16	217969_at	melanoma antigen, family D, 1	MAGED 1	NR	A cancer/testis antigen	Cancer Antigen
17	215733_x_at	cancer/testis antigen 2	CTAG2	NR	A cancer/testis antigen	Cancer Antigen
18	210546_x_at	cancer/testis antigen 1	CTAG1	NR	A cancer/testis antigen	Cancer Antigen
19	211674_x_at	cancer/testis antigen 1	CTAG1	NR	A cancer/testis antigen	Cancer Antigen
20	223313_s_at	MAGE-E1 protein	MAGE-E1	R	A cancer/testis antigen	Cancer Antigen
21	210467_x_at	melanoma antigen, family A, 12	MAGEA 12	NR	A cancer/testis antigen	Cancer Antigen
22	220057_at	GAGED2: G antigen, family D, 2	GAGED 2	NR	A cancer/testis antigen	Cancer Antigen
23	236152_at	PAGE-5 protein	PAGE-5	NR	A cancer/testis antigen	Cancer Antigen

24	233831_at	Homo sapiens serologically defined breast cancer antigen NY-BR-40 mRNA, partial cds	---	R	A breast cancer antigen	Cancer Antigen
25	206427_s_at	melan-A	MLANA	R	A cancer/testis antigen recognized by cytotoxic T-lympohocytes	Cancer Antigen
26	206218_at	melanoma antigen, family B, 2	MAGEB2	NR	A cancer/testis antigen	Cancer Antigen
27	203386_at	TBC1 domain family, member 4	TBC1D4	R	cancer antigen detected first in human sarcoma	Cancer Antigen
28	201457_x_at	BUB3 budding uninhibited by benzimidazoles 3 homolog (yeast)	BUB3	NR	mitotic spindle checkpoint component	Cell cycle
29	213348_at	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	CDKN1C	R	Cyclin-dependent kinase inhibitor 1C is a tight-binding inhibitor of several G1 cyclin/Cdk complexes and a negative regulator of cell proliferation. Mutations of CDKN1C are implicated in sporadic cancers and Beckwith-Wiedemann syndorome suggesting that it is a tumor suppressor candidate.	Cell cycle
30	204170_s_at	CDC28 protein kinase regulatory subunit 2	CKS2	NR	CKS2 protein binds to the catalytic subunit of the cyclin dependent kinases and is essential for their biological function. The CKS2 mRNA is found to be expressed in different patterns through the cell cycle in HeLa cells, which reflects specialized role for the encoded protein.	Cell cycle
31	206205_at	M-phase phosphoprotein 9	MPHOSPH9	NR	May be involveded in the progression from G2 to M phase in the cell cycle	Cell cycle
32	208796_s_at	cyclin G1	CCNG1	NR	The cyclin G1 gene has been identified as a target for transcriptional activation by the p53 tumor suppressor protein.	Cell cycle
33	204460_s_at	RAD1 homolog (S. pombe)	RAD1	NR	Has strong sequence homology to cell cycle checkpoint gene required for cell cycle arrest and DNA damage repair in response to DNA damage	Cell cycle
34	224918_x_at	microsomal glutathione S-transferase 1	MGST1	NR	MGST1 is a drug metabolizing enzyme involved in cellular defense against toxic electrophilic compounds. Localized to the endoplasmic reticulum and outer mitochondrial membrane where it is thought to protect these membranes from oxidative stress.	Drug metabolism

35	205998_x_at	cytochrome P450, subfamily IIIA (niphedipine oxidase), polypeptide 4	CYP3A4	R	Expression is induced by glucocorticoids and some pharmacological agents. This enzyme is involved in the metabolism of approximately half the drugs which are are used today, including acetaminophen, codeine, cyclosporin A, diazepam and erythromycin.	Drug metabolism
36	239476_at	phosphoinositide-3-kinase, regulatory subunit, polypeptide 1 (p85 alpha)	PIK3R1	R	PIK3R1: phosphoinositide-3-kinase, regulatory subunit, polypeptide 1 (p85 alpha);pro-apoptotic activity via suppression of the AKT survival pathway that is frequently activated in myeloma	Drug Resistance
37	211298_s_at	albumin	ALB	R	Albumin has been shown to acitivate the AKT signalling pathway and protect B-chronic lymphocytic leukemia patients from chlorambucil- and radiation-induced apoptosis	Drug Resistance
38	216835_s_at	docking protein 1, 62kDa (downstream of tyrosine kinase 1)	DOK1	R	Docking protein 1 is constitutively tyrosine phosphorylated in hematopoietic progenitors isolated from chronic myelogenous leukemia (CML) patients in the chronic phase. It may be a critical substrate for p210(bcr/abl), a chimeric protein whose presence is associated with CML.	Hematopoiesis
39	213891_s_at	TCF4	---	R	TCF4 is expressed predominantly in pre-B-cells, it is activated upon Wnt signalling	Hematopoiesis
40	212387_at	TCF4	---	R	TCF4 is expressed predominantly in pre-B-cells, it is activated upon Wnt signalling	Hematopoiesis
41	212382_at	TCF4: Transcription factor 4	---	R	TCF4 is expressed predominantly in pre-B-cells, it is activated upon Wnt signalling	Hematopoiesis
42	203753_at	transcription factor 4	TCF4	R	TCF4 is expressed predominantly in pre-B-cells, it is activated upon Wnt signalling	Hematopoiesis
43	212386_at	transcription factor 4	TCF4	R	TCF4 is expressed predominantly in pre-B-cells, it is activated upon Wnt signalling	Hematopoiesis
44	211709_s_at	stem cell growth factor; lymphocyte secreted C-type lectin	SCGF	R	SCGF is selectively produced by osseous and hematopoietic stromal cells, and can mediate their proliferative activity on primitive hematopoietic progenitor cells.	Hematopoiesis

45	217020 _at	---	---	R	Binds retinoic acid, the biologically active form of vitamin A which mediates cellular signalling in embryonic morphogenesis, cell growth and differentiation.	Mitogenic Signalling
46	217786 _at	SKB1 homolog (S. pombe)	SKB1	NR	may regulate mitosis through binding SHK1	Mitogenic Signalling
47	206109 _at	fucosyltransferase 1 (galactoside 2-alpha-L-fucosyltransferase, Bombay phenotype included)	FUT1	R	an essential component of Notch signalling pathway that regulate cell growth and differentiation	Mitogenic Signalling
48	227798 _at	MADH1 MAD, mothers against decapentaplegic homolog 1 (Drosophila)	---	NR	Involved in the TGF-beta signalling pathway, an important pathway that regulates cell growth, differentiation and apoptosis and is often disrupted in cancer.	Mitogenic Signalling
49	208743 _s_at	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide	YWHAB	NR	This gene encodes a protein belonging to the 14-3-3 family of proteins. It has been shown to interact with RAF1 and CDC25 phosphatases, suggesting that it may play a role in linking mitogenic signaling and the cell cycle machinery.	Mitogenic Signalling
50	225239 _at	ESTs, Moderately similar to hypothetical protein FLJ20958 [Homo sapiens] [H.sapiens]	---	R	SPRY4 is an inhibitor of the receptor-transduced mitogen-activated protein kinase (MAPK) signaling pathway, an important growth signalling pathway in cancer.	Mitogenic Signalling
51	215551 _at	estrogen receptor 1	ESR1	R	Estrogen receptor 1 alpha overexpression is implicated in breast and ovarian cancers, and activates the cyclin D1 pathway	Mitogenic Signalling
52	215067 _x_at	PRDX2: peroxiredoxin 2	---	R	PRDX2 may have a proliferative effect and play a role in cancer development or progression.	Mitogenic Signalling
53	210993 _s_at	MAD, mothers against decapentaplegic homolog 1 (Drosophila)	MADH1	NR	TGFB1 is the prototype of a large family of cytokines that also includes the activins (e.g., 147290), inhibins (e.g., 147380), bone morphogenetic proteins, and Mullerian-inhibiting substance (600957). Members of the TGF-beta family exert a wide range of biologic effects on a large variety of cell types; for example, they regulate cell growth, differentiation, matrix production, and apoptosis.	Mitogenic Signalling
54	209374 _s_at	immunoglobulin heavy constant mu	IGHM	NR	A surrogate marker of some types of multiple myeloma	Myeloma signalling

55	224342_x_at	immunoglobulin lambda locus	IGL@	NR	A surrogate marker of some types of multiple myeloma	Myeloma signalling
56	212827_at	immunoglobulin heavy constant mu	IGHM	NR	A surrogate marker of some types of multiple myeloma	Myeloma signalling
57	234366_x_at	immunoglobulin lambda locus	IGL@	R	A surrogate marker of some types of multiple myeloma	Myeloma signalling
58	216986_s_at	interferon regulatory factor 4	IRF4	NR	A mutliple myeloma oncogene, has been shown to regualte lymphocyte apoptosis by modulating the efficiency of the Fas signal	Myeloma signalling
59	205098_at	chemokine (C-C motif) receptor 1	CCR1	NR	studies suggest that chemokine receptor expression and the migratory capacity of MM cells to their ligands are relevant for the compartmentalization of MM cells in the bone marrow	Myeloma signalling
60	239237_at	ESTs	---	NR	Strong sequence similarity to Ig heavy chain, a surrogate marker for some types of multiple myeloma	Myeloma signalling
61	205099_s_at	chemokine (C-C motif) receptor 1	CCR1	NR	studies suggest that chemokine receptor expression and the migratory capacity of multiple myeloma cells to their ligands are relevant for the compartmentalization of multiple myeloma cells in the bone marrow	Myeloma signalling
62	223472_at	Wolf-Hirschhorn syndrome candidate 1	WHSC1	R	WHSC1 is involved in a chromosomal translocation t(4;14)(p16.3;q32.3) in multiple myelomas.	Myeloma translocation
63	222778_s_at	Wolf-Hirschhorn syndrome candidate 1	WHSC1	R	WHSC1 is involved in a chromosomal translocation t(4;14)(p16.3;q32.3) in multiple myelomas. Also, vv	Myeloma translocation
64	209054_s_at	Wolf-Hirschhorn syndrome candidate 1	WHSC1	R	WHSC1 is involved in a chromosomal translocation t(4;14)(p16.3;q32.3) in multiple myelomas.	Myeloma translocation
65	222777_s_at	Wolf-Hirschhorn syndrome candidate 1	WHSC1	R	WHSC1 is involved in a chromosomal translocation t(4;14)(p16.3;q32.3) in multiple myelomas. Also, vv	Myeloma translocation
66	209053_s_at	Wolf-Hirschhorn syndrome candidate 1	WHSC1	R	WHSC1 is involved in a chromosomal translocation t(4;14)(p16.3;q32.3) in multiple myelomas. Also, vv	Myeloma translocation

67	200921 _s_at	B-cell translocation gene 1, anti-proliferative	BTG1	NR	The BTG1 gene locus has been shown to be involved in a t(8;12)(q24;q22) chromosomal translocation in a case of B-cell chronic lymphocytic leukemia. It is a member of a family of antiproliferative genes. BTG1 expression is maximal in the G0/G1 phases of the cell cycle and downregulated when cells progressed through G1. It negatively regulates cell proliferation.	Myeloma translocation
68	209052 _s_at	Wolf-Hirschhorn syndrome candidate 1	WHSC1	R	WHSC1 is involved in a chromosomal translocation t(4;14)(p16.3;q32.3) in multiple myelomas.	Myeloma translocation
69	213940 _s_at	formin binding protein 1(FBP17)	FNBP1	NR	The human formin-binding protein 17 (FBP17) interacts with sorting nexin, SNX2, and is an MLL-fusion partner in acute myelogeneous leukemia	Myeloma translocation
70	213732 _at	transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47)	TCF3	R	The E2A gene maps to 19p13.3-p13.2, a site associated with nonrandom translocations in acute lymphoblastic leukemias.	Myeloma translocation
71	213047 _x_at	SET translocation (myeloid leukemia-associated)	SET	NR	The SET translocation (6;9)(p23q34) is the hallmark of a specific subtype of acute myeloid leukemia (AML) characterized by a poor prognosis and a young age of onset. SET protein regulates G(2)/M transition by modulating cyclin B-CDK1 activity.	Myeloma translocation
72	200631 _s_at	SET translocation (myeloid leukemia-associated)	SET	NR	The SET translocation (6;9)(p23q34) is the hallmark of a specific subtype of acute myeloid leukemia (AML) characterized by a poor prognosis and a young age of onset. SET protein regulates G(2)/M transition by modulating cyclin B-CDK1 activity.	Myeloma translocation
73	205068 _s_at	GTPase regulator associated with focal adhesion kinase pp125(FAK)	GRAF	R	GTPase regulator associated with the focal adhesion kinase pp125(FAK) is often involved in a translocations with the MLL gene in hematologic malignancies	Myeloma translocation
74	220146 _at	toll-like receptor 7	TLR7	NR	Expression of TLR7 may activate NF-kB, an important mediator of cell survival, and possible downstream target of proteasome inhibition	NFkB pathway
75	232304 _at	pellino homolog 1 (Drosophila)	PELI1	R	Pellino 1 is required for NF kappa B activation and IL-8 gene expression in response to IL-1	NFkB pathway

76	232213 _at	pellino homolog 1 (Drosophila)	PELI1	R	Pellino 1 is required for NF kappa B activation and IL-8 gene expression in response to IL-1	NFkB pathway
77	218319 _at	pellino homolog 1 (Drosophila)	PELI1	R	Pellino 1 is required for NF kappa B activation and IL-8 gene expression in response to IL-1	NFkB pathway
78	215744 _at	fusion, derived from t(12;16) malignant liposarcoma	FUS	R	Proto-oncoprotein resulting from fusion gene in myxoid liposarcoma; derived from t(12;16) malignant liposarcoma.	Oncogene
79	206363 _at	v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian)	MAF	R	MAF is a protooncogene	Oncogene
80	202768 _at	FBJ murine osteosarcoma viral oncogene homolog B	FOSB	R	The fos genes encode leucine zipper proteins that can dimerize with proteins of the JUN family, thereby forming the transcription factor complex AP-1. Thus, the FOS proteins have been implicated as regulators of cell proliferation, differentiation, and oncogenic transformation.	Oncogene
81	202647 _s_at	neuroblastoma RAS viral (v-ras) oncogene homolog	NRAS	NR	The N-ras oncogene is a member of the RAS gene family. It is mapped on chromosome 1, and it is activated in HL60, a promyelocytic leukemia line.	Oncogene
82	209640 _at	promyelocytic leukemia	PML	R	The expression of PML is cell-cycle related and it regulates the p53 response to oncogenic signals. The gene is often involved in the translocation with the retinoic acid receptor alpha gene associated with acute promyelocytic leukemia (APL).	Oncogene
140	232231 _at	Runt domain transcription factor	RUNX2	NR	Runt domain transcription factor AML3/RUNX2 is essential for the generation and differentiation of osteoblasts, and has been associated with the survival of several types of metastases in bone.	Oncogene
83	201575 _at	SKI-interacting protein	SNW1	NR	may be involved in oncogenesis since it interacts with a region of SKI oncoproteins that is required for transforming activity;overcomes the growth-suppressive activities of pRb	Oncogenic signalling
84	224985 _at	Homo sapiens, clone IMAGE:3446533, mRNA	---	NR	An oncogene involved in numerous cancers. A member of the RAS gene family.	Oncogenic signalling
85	204602 _at	dickkopf homolog 1 (Xenopus laevis)	DKK1	NR	A secreted inhibitor of WNT signalling, a pathway known to be important to oncogenesis	Oncogenic signalling

86	201653 _at	cornichon homolog (Drosophila)	CNIH	NR	may regulate EGF signalling, a pathway known to be involved in oncogenesis	Oncogenic signalling
87	234021 _at	Homo sapiens cDNA: FLJ21331 fis, clone COL02520.	---	R	highly similar to plakophilin 2 which associates with beta-catenin and up-regulates the oncogenic beta-catenin/T cell factor-signaling activity	Oncogenic signalling
88	212063 _at	CD44 antigen (homing function and Indian blood group system)	CD44	NR	The wide prevalence of CD44 cleavage suggests that it plays an important role in the pathogenesis of human tumors.	Oncogenic signalling
89	204489 _s_at	CD44 antigen (homing function and Indian blood group system)	CD44	NR	The wide prevalence of CD44 cleavage suggests that it plays an important role in the pathogenesis of human tumors.	Oncogenic signalling
90	227167 _s_at	Homo sapiens mesenchymal stem cell protein DSC96 mRNA, partial cds	---	NR	The RAS oncogene (MIM 190020) is mutated in nearly one-third of all human cancers. Members of the RAS superfamily are plasma membrane GTP-binding proteins that modulate intracellular signal transduction pathways. A subfamily of RAS effectors, including RASSF3, share a RAS association (RA) domain	Oncogenic signalling
91	202290 _at	PDGFA associated protein 1	PDAP1	NR	stimulates the inherent ATPase activity of Hsp90, a molecular chaperone that plays a key role in the conformational maturation of oncogenic signaling proteins	Oncogenic signalling
92	215499 _at	mitogen-activated protein kinase kinase 3 (MAP2K3)	MAP2K3	R	Expression of RAS oncogene is found to result in the accumulation of the active form of MAP2K3, which thus leads to the constitutive activation of MAPK14, and confers oncogenic transformation of primary cells.	Oncogenic signalling
93	200047 _s_at	YY1 transcription factor	YY1	NR	Some AML patients showed significantly elevated YY1 transcript levels in bone marrow cells. Taken together with mouse data, this suggests involvement in the pathogenesis of AML.	Oncogenic signalling
94	222555 _s_at	mitochondrial ribosomal protein L44	MRPL44	NR	involved in mitochondrial protein synthesis	Protein homeostasis
95	212694 _s_at	propionyl Coenzyme A carboxylase, beta polypeptide	PCCB	NR	may function in protein homeostasis via degradation of brached chain amino acids	Protein homeostasis
96	222530 _s_at	McKusick-Kaufman syndrome	MKKS	NR	similarity to the chaperonin family of proteins, suggesting a role for protein processing	Protein homeostasis

97	200869 _at	ribosomal protein L18a	RPL18A	NR	Ribosomes are involved in protein synthesis and thus contribute to protein homeostasis	Protein homeostasis
98	200023 _s_at	eukaryotic translation initiation factor 3, subunit 5 epsilon, 47kDa	EIF3S5	NR	Regulates initiation of protein translation and thus is involved in protein homeostasis	Protein homeostasis
99	200812 _at	chaperonin containing TCP1, subunit 7 (eta)	CCT7	NR	CCT regulates protein homeostasis via the folding of newly translated polypeptide substrates, including cyclin E	Protein homeostasis
100	225190 _x_at	ribosomal protein L35a	RPL35A	NR	Ribosomes are involved in protein synthesis and thus contribute to protein homeostasis	Protein homeostasis
101	200023 _s_at	eukaryotic translation initiation factor 3, subunit 5 epsilon, 47kDa	EIF3S5	NR	Regulates initiation of protein translation and thus is involved in protein homeostasis	Protein homeostasis
102	217919 _s_at	mitochondrial ribosomal protein L42	MRPL42	NR	involved in mitochondrial protein synthesis	Protein homeostasis
103	211972 _x_at	ribosomal protein, large, P0	RPLP0	NR	Ribosomes are involved in protein synthesis and thus contribute to protein homeostasis	Protein homeostasis
104	200024 _at	ribosomal protein S5	RPS5	NR	Ribosomes are involved in protein synthesis and thus contribute to protein homeostasis	Protein homeostasis
105	200715 _x_at	ribosomal protein L13a	RPL13A	NR	Ribosomes are involved in protein synthesis and thus contribute to protein homeostasis	Protein homeostasis
106	201258 _at	ribosomal protein S16	RPS16	NR	Ribosomes are involved in protein synthesis and thus contribute to protein homeostasis	Protein homeostasis
107	200003 _s_at	ribosomal protein L28	RPL28	NR	Ribosomes are involved in protein synthesis and thus contribute to protein homeostasis	Protein homeostasis
108	221726 _at	ribosomal protein L22	RPL22	NR	Ribosomes are involved in protein synthesis and thus contribute to protein homeostasis	Protein homeostasis
109	200041 _s_at	HLA-B associated transcript 1	BAT1	R	Members of this family are involved in a number of cellular functions including initiation of translation, RNA splicing, and ribosome assembly and thus could have a role in protein homeostasis.	Protein homeostasis

110	211937_at	eukaryotic translation initiation factor 4B	EIF4B	NR	Regulates initiation of protein translation and thus is involved in protein homeostasis	Protein homeostasis
111	200082_s_at	ribosomal protein S7	RPS7	NR	Ribosomes are involved in protein synthesis and thus contribute to protein homeostasis	Protein homeostasis
112	214167_s_at	ribosomal protein, large, P0	RPLP0	NR	Ribosomes are involved in protein synthesis and thus contribute to protein homeostasis	Protein homeostasis
113	200024_at	ribosomal protein S5	RPS5	NR	Ribosomes are involved in protein synthesis and thus contribute to protein homeostasis	Protein homeostasis
114	217719_at	eukaryotic translation initiation factor 3, subunit 6 interacting protein	EIF3S6IP	NR	Regulates initiation of protein translation and thus is involved in protein homeostasis	Protein homeostasis
115	225797_at	mitochondrial ribosomal protein L54	MRPL54	NR	involved in mitochondrial protein synthesis	Protein homeostasis
116	200937_s_at	ribosomal protein L5	RPL5	NR	Ribosomes are involved in protein synthesis and thus contribute to protein homeostasis	Protein homeostasis
117	208985_s_at	eukaryotic translation initiation factor 3, subunit 1 alpha, 35kDa	EIF3S1	NR	Regulates initiation of protein translation and thus is involved in protein homeostasis	Protein homeostasis
118	200834_s_at	ribosomal protein S21	RPS21	NR	Ribosomes are involved in protein synthesis and thus contribute to protein homeostasis	Protein homeostasis
119	216153_x_at	reversion-inducing-cysteine-rich protein with kazal motifs	RECK	R	The protein encoded by this gene is a cysteine-rich, extracellular protein with protease inhibitor-like domains whose expression is suppressed strongly in many tumors and cells transformed by various kinds of oncogenes. In normal cells, this membrane-anchored glycoprotein may serve as a negative regulator for matrix metalloproteinase-9, a key enzyme involved in tumor invasion and metastasis.	Tumor Supressor Pathway
120	217687_at	adenylate cyclase 2 (brain)	ADCY2	R	Adenylate cyclase signalling regulates cell growth and differentiation; it is frequently defective in human tumors. Activation of human Adenylyl Cyclase protein(s) and inhibition of human Pde4 protein protein(s) increase apoptosis of acute lymphoblastic leukemia cells	Tumor Supressor Pathway

121	222632 _s_at	leucine zipper transcription factor-like 1	LZTFL1	NR	The LZTFL1 gene has been mapped to a putative tumor suppressor region (C3CER1) on chromosome 3p21.3	Tumor Supressor Pathway
122	236623 _at	ATPase, Na+/K+ transporting, alpha 1 polypeptide	ATP1A1	R	Expression regulated by p53, a tumor supressor gene	Tumor Supressor Pathway
123	221899 _at	hypothetical protein from BCRA2 region	CG005	R	Located in the region of BRCA2, a breast cancer susceptibility gene	Tumor Supressor Pathway
124	221691 _x_at	nucleophosmin (nucleolar phosphoprotein B23, numatrin)	NPM1	NR	Nucleophosmin regulates the stability and transcriptional activity of p53	Tumor Supressor Pathway
125	209030 _s_at	immunoglobulin superfamily, member 4 (TSLC1)	IGSF4	NR	TSCL1 has been identified as a potential tumor supressor gene in lung cancer	Tumor Supressor Pathway
126	222762 _x_at	LIM domains containing 1 (LIMD1)	LIMD1	NR	Interstitial deletions of the short arm of chromosome 3 containing LIMD1 are found in a large number of tumors. IT may have a role as a tumor supressor.	Tumor Supressor Pathway
127	240983 _s_at	cysteinyl-tRNA synthetase	CARS	NR	This gene is one of several located near the imprinted gene domain of 11p15.5, an important tumor-suppressor gene region. Alterations in this region have been associated with the Beckwith-Wiedemann syndrome, Wilms tumor, rhabdomyosarcoma, adrenocortical carcinoma, and lung, ovarian, and breast cancer.	Tumor Supressor Pathway
128	200713 _s_at	microtubule-associated protein, RP/EB family, member 1	MAPRE 1	NR	MAPRE1 binds to the APC protein which is often mutated in familial and sporadic forms of colorectal cancer. This protein localizes to microtubules, especially the growing ends, in interphase cells. During mitosis, the protein is associated with the centrosomes and spindle microtubules.	Tumor Supressor Pathway
129	200814 _at	proteasome (prosome, macropain) activator subunit 1 (PA28 alpha)	PSME1	NR	subunit of the 11S regulator of the 20S proteasome	Ubiquitin/ proteasome pathway
130	201532 _at	proteasome (prosome, macropain) subunit, alpha type, 3	PSMA3	NR	core subunit of the proteasome	Ubiquitin/ proteasome pathway

131	218011_at	ubiquitin-like 5	UBL5	NR	Ubiquitin-like proteins (UBLs) are thought to be reversible modulators of protein function rather than protein degraders like ubiquitin	Ubiquitin/ proteasome pathway
132	224747_at	hypothetical protein LOC92912	LOC92912	NR	Contains a ubiquitin conjugating enzyme domain	Ubiquitin/ proteasome pathway
133	201758_at	tumor susceptibility gene 101	TSG101	NR	The protein encoded by this gene belongs to a group of apparently inactive homologs of ubiquitin-conjugating enzymes. The gene product contains a coiled-coil domain that interacts with stathmin, a cytosolic phosphoprotein implicated in tumorigenesis. The protein may play a role in cell growth and differentiation and act as a negative growth regulator.	Ubiquitin/ proteasome pathway
134	200019_s_at	Finkel-Biskis-Reilly murine sarcoma virus (FBR-MuSV) ubiquitously expressed (fox derived); ribosomal protein S30	FAU	NR	A fusion protein consisting of the ubiquitin-like protein fubi at the N terminus and ribosomal protein S30 at the C terminus. It has been proposed that the fusion protein is post-translationally processed to generate free fubi and free ribosomal protein S30. Fubi is a member of the ubiquitin family, and ribosomal protein S30 belongs to the S30E family of ribosomal proteins.	Ubiquitin/ proteasome pathway
135	202346_at	huntingtin interacting protein 2	HIP2	NR	UBIQUITIN-CONJUGATING ENZYME E2-25K has been implicated in the degradation of huntingtin and suppression of apoptosis.	Ubiquitin/ proteasome pathway
136	201177_s_at	SUMO-1 activating enzyme subunit 2	UBA2	NR	ubiquitin-like activating enzyme involved in protein homeostasis	Ubiquitin/ proteasome pathway
154	218438_s_at	endothelial-derived gene 1	EG1	NR	expressed in tumor-stimulated endothelial cells ; may have role in tumor angiogenesis	
157	216288_at	cysteinyl leukotriene receptor 1	CYSLTR1	R	upregulated in colon cancer; affecting survival	
166	210497_x_at	synovial sarcoma, X breakpoint 2	SSX2	NR	A cancer antigen involved in a translocation in synovial sarcoma. May be ionvolved in transcriptional repression.	
167	223358_s_at	phosphodiesterase 7A	PDE7A	NR	Increased PDE7 in T cells correlated with decreased cAMP, increased interleukin-2 expression, and increased proliferation.	

213	226882_x_at	WD repeat domain 4	WDR4	NR	Members of this family are involved in a variety of cellular processes, including cell cycle progression, signal transduction, apoptosis, and gene regulation.	
242	225647_s_at	cathepsin C	CTSC	NR	a lysosomal cysteine proteinase that appears to be a central coordinator for activation of many serine proteinases in immune/inflammatory cells	
251	208642_s_at	X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining; Ku autoantigen, 80kDa)	XRCC5	NR	Invoved in DNA repair, a pathway important to cancer. Defects in this pathway can lead to cancer and overactivity of this pathway can lead to chemotherapeutic resistance in cancer cells	
286	37793_r_at	RAD51-like 3 (S. cerevisiae)	RAD51L3	R	Possibly invoved in DNA damage repair based on sequence homology	
333	218467_at	hepatocellular carcinoma susceptibility protein	HCCA3	NR	A novel full-length cDNA was cloned and differentiated, which was highly expressed in liver cancer tissues.	
346	209031_at	immunoglobulin superfamily, member 4	IGSF4	NR		
442	208013_s_at	acrosomal vesicle protein 1	ACRV1	R	a testis differentiation antigen	

Proteasome inhibitor resistant cell lines

[00255] In order to better understand the specific mechanism(s) by which proteasome inhibitors exert their apoptotic effects, as well as to elucidate mechanisms by which those effects may be subverted, bortezomib resistant tumor cell lines were generated. Tumor cell lines were treated with a very low dose of bortezomib (approximately 1/20 the LD50 – a dose that would kill 50% of the cells) for 24 hours. The drug was then removed and surviving cells were allowed to recover for 24 to 72 hours. This process was then repeated for multiple rounds with the bortezomib dose doubled each time. After cells had been dosed with 3-5 times the LD50, several individual cell lines were sub-cloned from single cell colonies. Subsequent analyses demonstrated that these lines exhibit 5-10 fold resistance to bortezomib and that this characteristic is stable over months in culture and unaffected by inhibitors of multi-drug resistance pumps. This strategy was applied to both ovarian tumor cell lines (OVCAR-3) and myeloma tumor cell lines (RPMI8226) and multiple sub-clones were characterized. The resistant cell lines were then subject to gene expression profiling using the Affymetrix U133 microarray. A comparison of genes differentially expressed in sensitive parental (S) versus resistant sub-clones (R) highlighted several genes that were also identified in analysis of sensitive and resistant myeloma biopsies. See table 8. The number identified in Table 8 corresponds to the marker number identification in Table 1. Such results not only highlight a potential relationship between expression of these genes and bortezomib sensitivity, but also support the validity of methods used to define response genes in clinical samples.

TABLE 8 Gene Identification in Proteasome Inhibition Sensitive / Resistant Cell Lines

No.	Probeset ID	Title	R/S	Ratio Resistant / Parental
156	202075_s_at	gb:NM_006227.1 /DEF=Homo sapiens phospholipid transfer protein (PLTP), mRNA. /FEA=mRNA /GEN=PLTP /PROD=phospholipid transfer protein /DB_XREF=gi:5453913 /UG=Hs.283007 phospholipid transfer protein /FL=gb:L26232.1 gb:NM_006227.1	S	0.36
166	210497_x_at	gb:BC002818.1 /DEF=Homo sapiens, Similar to synovial sarcoma, X breakpoint 2, clone MGC:3884, mRNA, complete cds. /FEA=mRNA /PROD=Similar to synovial sarcoma, X breakpoint 2 /DB_XREF=gi:12803942 /UG=Hs.289105 synovial sarcoma, X breakpoint 2 /FL=gb:BC002818.1	R	2.82

332	210715_s_at	gb:AF027205.1 /DEF=Homo sapiens Kunitz-type protease inhibitor (kop) mRNA, complete cds. /FEA=mRNA /GEN=kop /PROD=Kunitz-type protease inhibitor /DB_XREF=gi:2598967 /UG=Hs.31439 serine protease inhibitor, Kunitz type, 2 /FL=gb:AF027205.1	S	0.37
211	219373_at	gb:NM_018973.1 /DEF=Homo sapiens dolichyl-phosphate mannosyltransferase polypeptide 3 (DPM3), mRNA. /FEA=mRNA /GEN=DPM3 /PROD=dolichyl-phosphate mannosyltransferasepolypeptide 3 /DB_XREF=gi:9506552 /UG=Hs.110477 dolichyl-phosphate mannosyltransferase polypeptide 3 /FL=gb:AF312923.1 gb:AF312922.1 gb:AB028128.1 gb:NM_018973.1	S	0.37
343	200030_s_at	gb:NM_002635.1 /DEF=Homo sapiens solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 3 (SLC25A3), nuclear gene encoding mitochondrial protein, transcript variant 1b, mRNA. /FEA=mRNA /GEN=SLC25A3 /PROD=phosphate carrier precursor isoform 1b /DB_XREF=gi:4505774 /UG=Hs.78713 solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 3 /FL=gb:BC000998.1 gb:BC001328.1 gb:BC003504.1 gb:BC004345.1 gb:NM_002635.1	R	2
447	222975_s_at	Consensus includes gb:AI423180 /FEA=EST /DB_XREF=gi:4269111 /DB_XREF=est:tf32e08.x1 /CLONE=IMAGE:2097926 /UG=Hs.69855 NRAS-related gene /FL=gb:AB020692.1	R	1.16
280	224673_at	Consensus includes gb:AI613244 /FEA=EST /DB_XREF=gi:4622411 /DB_XREF=est:ty35a06.x1 /CLONE=IMAGE:2281042 /UG=Hs.306121 leukocyte receptor cluster (LRC) encoded novel gene 8	S	0.44
129	200814_at	gb:NM_006263.1 /DEF=Homo sapiens proteasome (prosome, macropain) activator subunit 1 (PA28 alpha) (PSME1), mRNA. /FEA=mRNA /GEN=PSME1 /PROD=proteasome (prosome, macropain) activatorsubunit 1 (PA28 alpha) /DB_XREF=gi:5453989 /UG=Hs.75348 proteasome (prosome, macropain) activator subunit 1 (PA28 alpha) /FL=gb:BC000352.1 gb:L07633.1 gb:NM_006263.1	R	2.11
390	204610_s_at	gb:NM_006848.1 /DEF=Homo sapiens hepatitis delta antigen-interacting protein A (DIPA), mRNA. /FEA=mRNA /GEN=DIPA /PROD=hepatitis delta antigen-interacting protein A /DB_XREF=gi:5803004 /UG=Hs.66713 hepatitis delta antigen-interacting protein A /FL=gb:U63825.1 gb:NM_006848.1	R	2.09
429	222646_s_at	Consensus includes gb:AW268365 /FEA=EST /DB_XREF=gi:6655395 /DB_XREF=est:xv50d03.x1 /CLONE=IMAGE:2816549 /UG=Hs.25740 ERO1 (S. cerevisiae)-like /FL=gb:AF081886.1 gb:NM_014584.1	R	2.74

Sensitivity Assays

[00256] A sample of cancerous cells is obtained from a patient. An expression level is measured in the sample for a marker corresponding to at least one of the predictive markers set forth in Table 1, Table 2 and/or Table 3. Preferably a marker set is utilized comprising markers idenitifed in Table 1, Table 2 and/or Table 3 and put together in a marker set using the methods described herein. For example, marker sets can comprise the marker sets identified in Table 4, Table 5 and/or Table 6 or any marker set prepared by similar methods. Such analysis is used to obtain an expression profile of the tumor in the patient. Evaluation of the expression profile is then used to determine whether the patient is a responsive patient and would benefit from proteasome inhibition therapy (e.g., treatment with a proteasome inhibitor (e.g., bortezomib) alone, or in combination with additional agents). Evaluation can include use of one marker set prepared using any of the methods provided or other similar scoring methods known in the art (e.g., weighted voting, CTF). Still further, evaluation can comprise use of more than one prepared marker set. A proteasome inhibition therapy will be identified as appropriate to treat the cancer when the outcome of the evaluation demonstrates decreased non-responsiveness or increased responsiveness in the presence of the agent.

[00257] Examining the expression of one or more of the identified markers or marker sets in a tumor sample taken from a patient during the course of proteasome inhibition treatment, it is also possible to determine whether the therapeutic agent is continuing to work or whether the cancer has become non-responsive (refractory) to the treatment protocol. For example, a patient receiving a treatment of bortezomib would have tumor cells removed and monitored for the expression of the a marker or marker set. If the expression profile of one or more marker sets identified in Table 1, Table 2 and/or Table 3 demonstrates increased responsiveness in the presence of the agent, the treatment with proteasome inhibitor would continue. However, if the expression profile of one or more marker sets identified in Table 1, Table 2 or Table 3 demonstrates increased non-responsiveness in the presence of the agent, then the cancer may have become resistant to proteasome inhibition therapy and another treatment protocol should be initiated to treat the patient.

[00258] Importantly, these determinations can be made on a patient by patient basis or on an agent by agent (or combinations of agents). Thus, one can determine whether or not a

particular proteasome inhibition therapy is likely to benefit a particular patient or group/class of patients, or whether a particular treatment should be continued.

Other Embodiments

[00259] The present invention is not to be limited in scope by the specific embodiments described that are intended as single illustrations of aspects of the invention. Functionally equivalent methods and components are within the scope of the invention, in addition to those shown and described herein and will become apparent to those skilled in the art from the foregoing description, using no more than routine experimentation. Such equivalents are intended to be encompassed by the following claims.

[00260] All references cited herein, including journal articles, patents, and databases are expressly incorporated by reference.

[00261] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[00262] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for determining a proteasome inhibition therapy regimen for treating a tumor in a patient comprising:

a) determining the level of expression of markers in a marker set comprising at least two predictive markers selected from the group consisting of the markers identified in Table 1, Table 2 and Table 3, in a patient sample comprising tumor cells; and

b) determining a proteasome inhibition-based regimen for treating the tumor based on the expression of the predictive markers, wherein a significant expression level of the marker set is indicative that the patient is either a responsive patient or a non-responsive patient.

2. A method for treating a tumor in a patient with a proteasome inhibition therapy comprising:

a) determining the level of expression of markers in a marker set comprising at least two predictive markers selected from the group consisting of the markers identified in Table 1, Table 2 and Table 3, in a patient sample comprising tumor cells; and

b) treating the patient with proteasome inhibition therapy comprising a proteasome inhibitor agent based on the expression of the predictive markers, wherein a significant expression level of the marker set is indicative that the patient is a responsive patient.

3. The method of claim 1 or 2, wherein the level of expression of the predictive markers is determined by detection of mRNA or protein.

4. The method of any one of claims 1 to 3, wherein the proteasome inhibition-based regimen for treating the tumor comprises treatment with bortezomib.

5. The method of any one of claims 1 to 4, wherein the predictive markers are selected from the markers identified in any of Table 4, Table 5, Table 6 or Table 7.

6. The method of any one of claims 1 to 5, wherein determining the significant level of expression is determined by comparison with a control marker or by comparison to a predetermined standard.

7. The method of any one of claims 1 to 6, wherein the tumor is selected from liquid or solid tumors.

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8. The method of claim 7, wherein the liquid tumor is selected from the group consisting of multiple myeloma, Non-Hodgkins Lymphoma, B-cell lymphomas, mantle cell lymphoma, Waldenstrom's syndrome, chronic lymphocytic leukemia, and other leukemias.

9. The method of any one of claims 1 to 8, wherein the proteasome inhibition-based regimen for treating the tumor comprises treatment with a proteasome inhibitor that is selected from the group consisting of a peptidyl aldehyde, a peptidyl boronic acid, a peptidyl boronic ester, a vinyl sulfone, an epoxyketone, and a lactacystin analog.

10. The method of any one of claims 1 to 9, wherein the patient sample comprising tumor cells is obtained from the subject any time selected from prior to tumor therapy, concurrently with tumor therapy or after tumor therapy.

11. A marker set when used in the method of any one of claims 1 to 10 comprising at least two isolated nucleic acid molecules selected from Table 1, Table 2 or Table 3.

12. The marker set of claim 11 comprising a marker set constructed using the weighted voting method or the combination of threshold features method.

13. A kit when used in the method of any one of claims 1 to 10 comprising reagents for assessing the expression of at least one predictive marker, and instructions for use.

14. The kit of claim 13 wherein the reagents comprise one or a plurality of nucleic acid probes, wherein the probe specifically binds at least one predictive marker.

15. The kit of claim 13 wherein the reagents comprise at least one detecting reagent selected from the group consisting of an antibody, an antibody derivative, an antibody fragment, and peptide probe, wherein the antibody, antibody derivative, antibody fragment or peptide probe specifically binds to a protein corresponding to at least one predictive marker.

16. The method of any one of claims 1 to 10, wherein the at least one predictive marker is associated with a biological function selected from the group consisting of cellular adhesion, apoptotic signaling, cell cycle, drug metabolism, drug resistance, growth control, hematopoesis, mitogenic signaling, myeloma signaling, myeloma translocation, NFkB pathway, oncogenes, oncogenic signaling, protein homeostasis, tumor suppressor pathway, and the ubiquitin/proteasome pathway, or is a cancer antigen.

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17. The method of any one of claims 1 to 10, wherein the predictive markers are selected from Table 1, Table 2 or Table 3 by using the weighted voting method or combination of threshold features method.

18. The marker set of claim 11 or 12, wherein the marker set consists of the markers in any of Table 4, Table 5 or Table 6.

19. The method of any one of claims 1 to 10, 16 or 17, the marker set of any one of claims 11, 12 or 18, or the kit of any one of claims 13 to 15, substantially as hereinbefore described.