[0005] Thus, there is a need for objective, reproducible methods for predicting treatment outcome such as progression free survival of cancer patients or for monitoring the progress of such treatment and thereby selecting the optimal treatment regimen for each patient.

Summary ~~of the Invention~~

[0006] The methods of the present ~~invention~~disclosure can be utilized in a variety of settings, including, for example, in aiding in methods of treating cancer patients or in patient selection during the course of drug development, prediction of likelihood of success when treating an individual patient with a particular treatment regimen, in assessing disease progression, in monitoring treatment efficacy, in determining prognosis for individual patients and in assessing predisposition of an individual to benefit from a particular anti-cancer therapy.

[0007] The present ~~invention~~disclosure is based, in part, on the discovery that expression levels of certain biomarkers in patients suffering from cancer correlate with reduced clinical benefit from anti-angiogenic therapy alone. Accordingly, in one ~~aspect~~embodiment the ~~invention~~disclosure provides a method of optimizing therapeutic efficacy for the treatment of cancer, comprising the step of detecting the expression level of placental growth factor (PlGF) in a sample obtained from the patient wherein increased expression of PlGF in the sample as compared to a reference sample indicates that the patient may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy. In some embodiments, the method further comprises administering an anti-cancer therapy to the patient, wherein the anti-cancer therapy is other than or in addition to the anti-angiogenic therapy.

[0008] In another ~~aspect~~embodiment the ~~invention~~disclosure provides a method of identifying a cancer patient who may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy, comprising the step of detecting the expression level of placental growth factor (PlGF) in a sample obtained from the patient wherein increased expression of PlGF in the sample as compared to a reference sample indicates that the patient may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy. In one embodiment, the sample from the patient is obtained before or at commencement of the anti-angiogenic therapy. In one embodiment, the sample from the patient is obtained after commencement of the anti-angiogenic therapy. In some embodiments, the method further comprises administering an anti-cancer therapy to the patient, wherein the anti-cancer therapy is other than or in addition to the anti-angiogenic therapy.

[0009] In another ~~aspect~~embodiment the ~~invention~~disclosure provides a method of predicting responsiveness of a cancer patient to anti-angiogenic therapy comprising determining the expression level of PlGF in a sample obtained from the patient wherein increased expression levels of PlGF as compared to a reference sample indicates that the patient is less likely to be responsive to the anti-angiogenic therapy alone. In one embodiment, the sample from the patient is obtained before or at commencement of the anti-angiogenic therapy. In one embodiment, the sample from the patient is obtained after commencement of the anti-angiogenic therapy. In some embodiments, the method further comprises administering an anti-cancer therapy to the patient, wherein the anti-cancer therapy is other than or in addition to the anti-angiogenic therapy.

[0010] The ~~invention~~disclosure also provides a method of treating a patient with cancer comprising administering to the patient an anti-cancer therapy other than or in addition to anti-angiogenic therapy, wherein a sample obtained from the patient shows increased expression levels of PlGF as compared to a reference sample. In one embodiment, the sample from the patient is obtained before or at commencement of the anti-angiogenic therapy. In one embodiment, the sample from the patient is obtained after commencement of the anti-angiogenic therapy. The sample may be obtained from the patient before commencement of treatment. In one embodiment the sample has a PlGF expression level of greater than or equal to 28 pg/ml. In some embodiments the sample may be obtained from a patient currently being treated with anti-angiogenic therapy. In one embodiment, the sample from the patient is obtained after commencement of the anti-angiogenic therapy. In one embodiment the sample has a PlGF expression level of greater than or equal to 50 pg/ml.

[0011] In another ~~aspect~~embodiment the ~~invention~~disclosure provides a method of treating a cancer patient comprising administering to the patient an anti-angiogenic therapy, wherein a sample obtained from the patient shows low or decreased expression levels of PlGF as compared to a reference sample. The sample may be obtained from the patient before commencement of treatment. In one embodiment the sample has a PlGF expression level of less than or equal to 28 pg/ml. In some embodiments the sample may be obtained from a patient currently being treated with anti-angiogenic therapy. In one embodiment, the sample from the patient is obtained after commencement of the anti-angiogenic therapy. In one embodiment the sample has a PlGF expression level of less than or equal to 50 pg/ml. In some embodiments, the anti-angiogenic therapy comprises administration of an anti-VEGF antibody, e.g., bevacizumab.

[0011a] In one aspect, there is provided a use of an anti-cancer therapy other than or in addition to anti-angiogenic therapy comprising an anti-VEGF antibody in a method of treating a patient suffering from breast cancer, the method comprising: determining an expression level of PlGF in a sample that

has been obtained from the patient, wherein an increased expression level of PlGF in the sample that has been obtained from the patient as compared to a reference sample identifies the patient as one who may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy comprising an anti-VEGF antibody.

[0011b] In another aspect, there is provided a use of an anti-cancer therapy other than or in addition to anti-angiogenic therapy comprising an anti-VEGF antibody in the manufacture of a medicament for treating a patient suffering from breast cancer, the treating comprising: determining an expression level of PlGF in a sample that has been obtained from the patient, wherein an increased expression level of PlGF in the sample that has been obtained from the patient as compared to a reference sample identifies the patient as one who may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy comprising an anti-VEGF antibody.

[0011c] In another aspect, there is provided a kit for identifying a patient suffering from breast cancer who may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy comprising an anti-VEGF antibody by detecting expression levels of PlGF, the kit comprising: a compound capable of specifically detecting expression levels of PlGF; and instructions for using the kit to predict responsiveness of a patient suffering from breast cancer to anti-angiogenic therapy comprising an anti-VEGF antibody alone, wherein increased expression of PlGF as compared to a reference sample indicates that the patient may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy comprising an anti-VEGF antibody.

[0012] Also provided are kits comprising a compound capable of specifically detecting expression levels of PlGF, wherein the kit further comprises instructions for using the kit to predict responsiveness of a patient suffering from cancer to anti-angiogenic therapy alone, wherein increased expression of PlGF as compared to a reference sample indicates that the patient may benefit from anti-cancer therapy other than or in addition to the anti-angiogenic therapy.

[0013] In any of the methods described herein, the sample may be a tissue or cell sample or obtained from blood, plasma and/or serum. In certain embodiments the sample is obtained from the patient before commencement of treatment of the cancer. In certain embodiments the sample is obtained from the patient after commencement of treatment of the cancer. For example, the sample is obtained within 24 hours after beginning cancer treatment or within 2, 3, 5, 10, 14, 20, 25, 28, 42, or 56 days after commencement of cancer treatment.

[0014] In any of the methods described herein, expression levels of the one or more genes or gene products can be determined at the nucleic acid level, protein level or secretion or surface expression level of the protein. In certain embodiments the increase in expression levels of PlGF is an increase of 1.4-1.8 fold in expression level. In some embodiments the increase in expression levels of PlGF is an increase of at least 1.5 fold in expression level.

[0015] In some embodiments of the methods of the ~~invention~~disclosure, the cancer is carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers include squamous cell cancer, lung cancer (including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung), cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer (including gastrointestinal cancer), pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia); chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia;

and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors) or Meigs' syndrome.

[0016] In one embodiment the cancer is breast cancer, including, e.g., metastatic breast cancer.

[0017] The methods of the ~~invention~~disclosure can be performed with any anti-cancer agent described herein below. The anti-angiogenic agent may be any of the anti-angiogenesis agents described herein below, alone or in combination. In some embodiments the anti-angiogenic therapy comprises administration of VEGF antagonist, including, e.g., an anti-VEGF antibody. In some embodiments, the anti-VEGF antibody is bevazicumab.

[0018] Any embodiment described herein or any combination thereof applies to any and all methods of the invention described herein.

Brief Description of the Figures

[0019] **Figure 1** is a graph comparing overall survival of patients with breast cancer to plasma PlGF levels at Day 0 (before commencement of treatment).

[0020] **Figure 2** is a graph showing that plasma PlGF levels increased in response to treatment with bevacizumab.

[0021] **Figure 3** is a graph comparing overall survival of patients with breast cancer to plasma PlGF levels at Day 14 of treatment with bevacizumab.

Detailed Description

[0022] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, "Molecular Cloning: A Laboratory Manual", second edition (Sambrook et al., 1989); "Oligonucleotide Synthesis" (M. J. Gait, ed., 1984); "Animal Cell Culture" (R. I. Freshney, ed., 1987); "Methods in Enzymology" (Academic Press, Inc.); "Current Protocols in Molecular Biology" (F. M. Ausubel et al., eds., 1987, and periodic updates); "PCR: The Polymerase Chain Reaction", (Mullis et al., eds., 1994).

[0023] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this

What is claimed is:

1. Use of an anti-cancer therapy other than or in addition to anti-angiogenic therapy comprising an anti-VEGF antibody in a method of treating a patient suffering from breast cancer, the method comprising:

determining an expression level of PlGF in a sample that has been obtained from the patient,

wherein an increased expression level of PlGF in the sample that has been obtained from the patient as compared to a reference sample identifies the patient as one who may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy comprising an anti-VEGF antibody.

2. Use of an anti-cancer therapy other than or in addition to anti-angiogenic therapy comprising an anti-VEGF antibody in the manufacture of a medicament for treating a patient suffering from breast cancer, the treating comprising:

determining an expression level of PlGF in a sample that has been obtained from the patient,

wherein an increased expression level of PlGF in the sample that has been obtained from the patient as compared to a reference sample identifies the patient as one who may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy comprising an anti-VEGF antibody.

3. The use of claim 1 or 2, wherein the expression level of PlGF in the sample that has been obtained from the patient is increased at least about 1.5 fold as compared to a reference sample.

4. The use of claim 1 or 2, wherein the anti-VEGF antibody is bevacizumab.

5. The use of claim 1 or 2, wherein the breast cancer is metastatic breast cancer.

6. The use of claim 1 or 2, wherein the sample that has been obtained from the patient is selected from the group consisting of plasma, whole blood, serum, and combinations thereof.

7. The use of claim 1 or 2, wherein the expression level of PlGF is a protein expression level of PlGF.

8. The use of claim 1 or 2, wherein the sample is to be obtained from the patient prior to anti-angiogenic therapy.

9. The use of claim 1 or 2, wherein the sample is to be obtained from the patient after commencement of anti-angiogenic therapy.

10. The use of claim 9, wherein the sample is to be obtained from the patient within 24 hours after commencement of anti-angiogenic therapy.

11. The use of claim 9, wherein the sample is to be obtained from the patient within 14 days after commencement of anti-angiogenic therapy.

12. A kit for identifying a patient suffering from breast cancer who may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy comprising an anti-VEGF antibody by detecting expression levels of PlGF, the kit comprising:

a compound capable of specifically detecting expression levels of PlGF; and

instructions for using the kit to predict responsiveness of a patient suffering from breast cancer to anti-angiogenic therapy comprising an anti-VEGF antibody alone, wherein increased expression of PlGF as compared to a reference sample indicates that the patient may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy comprising an anti-VEGF antibody.

13. The kit of claim 12, wherein the anti-VEGF antibody is bevacizumab.

What is claimed is:

1. A method of identifying a patient suffering from cancer who may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy, comprising

determining expression level of placental growth factor (PlGF) in a sample obtained from the patient,

wherein increased expression level of PlGF in the sample obtained from the patient as compared to a reference sample indicates that the patient may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy.

2. A method of predicting responsiveness of a patient suffering from cancer to anti-angiogenic therapy comprising

determining expression level of PlGF in a sample obtained from the patient,

wherein increased expression level of PlGF in the sample obtained from the patient as compared to a reference sample indicates that the patient is less likely to be responsive to the anti-angiogenic therapy alone.

3. A method of monitoring effectiveness of an anti-angiogenic therapy comprising

determining expression level of PlGF in a sample obtained from the patient,

wherein increased expression level of PlGF in the sample obtained from the patient as compared to a reference sample indicates that the patient is less likely to be responsive to the anti-angiogenic therapy alone.

4. A method of optimizing therapeutic efficacy for treatment of cancer, the method comprising

determining expression level of PlGF in a sample obtained from the patient,

wherein increased expression level of PlGF in the sample obtained from the patient as compared to a reference sample indicates that the patient is less likely to be responsive to the anti-angiogenic therapy alone.

5. The method of any one of claims 1-4, wherein the expression level of PlGF in the sample obtained form the patient is increased at least about 1.5 fold as compared to a reference sample.

6. The method of any one of claims 1-4, wherein the anti-angiogenic therapy comprises administration of a VEGF antagonist.

7. The method of claim 6, wherein the VEGF antagonist is an anti-VEGF antibody.

8. The method of claim 7, wherein the anti-VEGF antibody is bevacizumab.

9. The method of claim 5, wherein the cancer is breast cancer.

10. The method of any one of claims 1-4, wherein the sample obtained from the patient is plasma.

11. The method of claim 10, wherein the expression level of PlGF is determined by detecting PlGF protein in the plasma.

12. The method of any one of claims 1-4, wherein the sample is obtained from the patient prior to anti-angiogenic therapy.

13. The method of any one of claims 1-4, wherein the sample is obtained from the patient after commencement of anti-angiogenic therapy.

14. The method of claim 12, wherein the sample is obtained from the patient within 24 hours after commencement of anti-angiogenic therapy.

15. The method of claim 12, wherein the sample is obtained from the patient within 14 days after commencement of anti-angiogenic therapy.

16. The method of any of claims 1-4, further comprising administering an anti-cancer therapy to the patient, wherein the anti-cancer therapy is other than or in addition to an anti-angiogenic therapy.

17. The method of claim 16, wherein the anti-cancer therapy is administered to the patient

when the expression level of PlGF in a sample obtained from the patient is increased compared to a reference sample.

18. A kit for detecting expression levels of PlGF, the kit comprising:

a compound capable of specifically detecting expression levels of PlGF; and

instructions for using said kit to predict responsiveness of a patient suffering from cancer to anti-angiogenic therapy alone, wherein increased expression of PlGF as compared to a reference sample indicates that the patient may benefit from anti-cancer therapy other than or in addition to anti-angiogenic therapy.