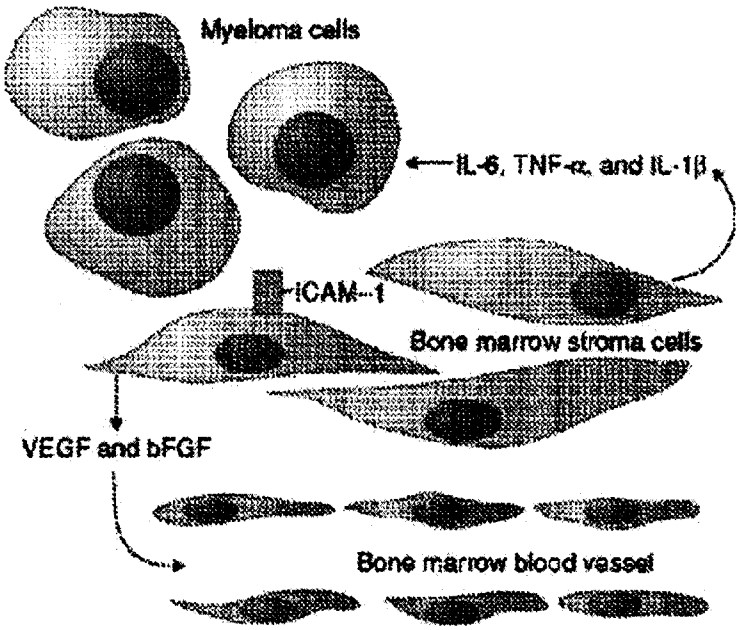
ORIGINAL

ABSTRACT

BIOMARKERS FOR PREDICTING THE SENSITIVITY AND RESPONSE OF PROTEIN KINASE CK2-MEDIATED DISEASES TO CK2 INHIBITORS

Disclosed are biomarkers for determining the sensitivity of protein kinase CK2-mediated diseases, such as proliferative and/or inflammatory disorders, to treatment with CK2 inhibitors. These biomarkers can be used to predict or select subjects likely to be responsive to treatment with a CK2 inhibitor, and to treat or monitor subjects undergoing treatment with a CK2 inhibitor.

FIGURE 1



I/We claim:

1. A method for monitoring the response of a subject being treated with a CK2 inhibitor, said method comprising:

(a) determining the level of a biomarker in a biological sample derived from the subject at a time point during or after administration of the CK2 inhibitor, wherein the biomarker is selected from the level of phosphorylated Akt S129, the ratio of phosphorylated Akt S 129 to total Akt, the level of phosphorylated Akt S473, the ratio of phosphorylated Akt S 473 to total Akt, the level of phosphorylated p21 T145, the ratio of phosphorylated p21 T145 to total p21, the level of phosphorylated NF-κB S529, the ratio of phosphorylated NF-κB S529 to total NF-κB, the level of phosphorylated STAT3 T705, the ratio of phosphorylated STAT3 T705 to total STAT3, the level of phosphorylated JAK2 Y1007/1008, and the ratio of phosphorylated JAK2 Y1007/1008 to total JAK2; and

(b) comparing the level of the biomarker in the biological sample with a reference level of the biomarker;

wherein a decrease in the level of the biomarker in the biological sample compared to the reference level of the biomarker is indicative of a positive response to treatment with said CK2 inhibitor.

2. The method of claim 1, wherein the reference level of the biomarker is selected from the group consisting of 1) the level of said biomarker from the subject prior to administration of the CK2 inhibitor; (2) the level of said biomarker from a reference population; (3) a pre-assigned level for said biomarker; and (4) the level of said biomarker from the subject at a second time point prior to the first time point.

3. The method of any of claims 1 or 2, wherein said biological sample is selected from a cell, a tissue, a tissue culture, a tumor, or a biological fluid derived from said subject.

4. The method of claim 3, wherein said biological fluid is selected from plasma, serum, or PBMCs.

5. The method of claim 3, wherein said cell is a circulating tumor cell (CTC).

6. The method of any of claims 1 or 2, wherein said subject suffers from a cancer or malignancy.

7. The method of claim 6, wherein said cancer or malignancy is selected from breast cancer, inflammatory breast cancer (IBC), pancreatic cancer, prostate cancer, lung cancer, colon cancer, melanoma, and multiple myeloma.

8. The method of any of claims 1 or 2, wherein said subject suffers from a CK-2 mediated autoimmune, inflammatory, or infectious disorder.

9. The method of any of claims 1 or 2, wherein said CK2 inhibitor is CX-4945.

10. A method for monitoring the response of a subject being treated with a CK2 inhibitor, said method comprising:

(a) determining the level of mRNA and/or protein expression of a biomarker in a biological sample derived from the subject at a time point during or after administration of the CK2 inhibitor, wherein the biomarker is selected from IL-6, IL-8, CK2α, CK2α', CK2β, VEGF, and HIF-1α; and

(b) comparing the level of the biomarker in the biological sample with a reference level of the biomarker;

wherein a decrease in the level of the biomarker in the biological sample compared to the reference level of the biomarker is indicative of a positive response to treatment with said CK2 inhibitor.

11. The method of claim 10, wherein the reference level of the biomarker is selected from the group consisting of 1) the level of said biomarker from the subject prior to administration of the CK2 inhibitor; (2) the level of said biomarker from a reference population; (3) a pre-assigned level for said biomarker; and (4) the level of said biomarker from the subject at a second time point prior to the first time point.

12. The method of any of claims 10 or 11, wherein said biological sample is selected from a cell, a tissue, a tissue culture, a tumor, or a biological fluid derived from said subject.

13. The method of claim 12, wherein said biological fluid is selected from plasma, serum, or PBMCs.

14. The method of claim 12, wherein said cell is a circulating tumor cell (CTC).

15. The method of any of claims 10 or 11, wherein said subject suffers from a cancer or malignancy.

16. The method of claim 15, wherein said cancer or malignancy is selected from breast cancer, inflammatory breast cancer (IBC), pancreatic cancer, prostate cancer, lung cancer, colon cancer, melanoma, and multiple myeloma.

17. The method of any of claims 10 or 11, wherein said subject suffers from a CK-2 mediated autoimmune, inflammatory, or infectious disorder.

18. The method of any of claims 10 or 11, wherein said CK2 inhibitor is CX-4945.

19. A method for predicting the clinical response of a CK2-mediated disease to treatment with a CK2 inhibitor in a subject, said method comprising determining the level of one or more biomarkers in a biological sample derived from the subject, wherein an elevated level of said one or more biomarkers relative to a control biological sample is indicative of sensitivity of the CK2-mediated disease to treatment with said CK2 inhibitor, and wherein said biomarker is selected from the level of phosphorylated Akt S129, the ratio of phosphorylated Akt S 129 to total Akt, the level of phosphorylated Akt S473, the ratio of phosphorylated Akt S 473 to total Akt, the level of phosphorylated p21 T145, the ratio of phosphorylated p21 T145 to total p21, the level of phosphorylated NF-κB S529, the ratio of phosphorylated NF-κB S529 to total NF-κB, the level of phosphorylated STAT3 T705, the ratio of phosphorylated STAT3 T705 to total STAT3, the level of phosphorylated JAK2 Y1007/1008, the ratio of phosphorylated JAK2 Y1007/1008 to total JAK2, the expression level of IL-6, the expression level of IL-8, the expression level of CK2α, the expression level of CK2α', the expression level of CK2β, the expression level of VEGF, and the expression level of HIF-1α.

20. The method of claim 19, wherein said biological sample is selected from a cell, a tissue, a tissue culture, a tumor, or a biological fluid derived from said subject.

21. The method of claim 20, wherein said biological fluid is selected from plasma, serum, or PBMCs.

22. The method of claim 20, wherein said cell is a circulating tumor cell (CTC).

23. The method of claim 19, wherein said subject suffers from a cancer or malignancy.

24. The method of claim 23, wherein said cancer or malignancy is selected from breast cancer, inflammatory breast cancer (IBC), pancreatic cancer, prostate cancer, lung cancer, colon cancer, melanoma, and multiple myeloma.

25. The method of claim 19, wherein said subject suffers from a CK-2 mediated autoimmune, inflammatory, or infectious disorder.

26. The method of claim 19, wherein said CK2 inhibitor is CX-4945.

27. A method for predicting the clinical response of a cancer or malignancy to treatment with a CK2 inhibitor in a subject, said method comprising:

(a) determining the level of CK2α' mRNA and/or protein expression in a biological sample derived from the subject; and

(b) determining the level of p-Akt S129 and/or the ratio of p-Akt S129 to total Akt in a biological sample derived from the subject;

wherein a positive correlation between the level of CK2α' mRNA and/or protein expression and the level of p-Akt S129 and/or ratio of p-Akt S129 to total Akt is indicative of sensitivity of the cancer or malignancy to treatment with said CK2 inhibitor.

28. The method of claim 27, wherein said biological sample is selected from a cell, a tissue, a tissue culture, a tumor, or a biological fluid derived from said subject.

29. The method of claim 28, wherein said biological fluid is selected from plasma, serum, or PBMCs.

30. The method of claim 27, said cancer or malignancy is breast cancer, inflammatory breast cancer (IBC), or multiple myeloma.

31. The method of claim 27, wherein said CK2 inhibitor is CX-4945.

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To,
The Controller of Patents
The Patent Office at **New Delhi**