

We Claim:

1. The use of an anti-cancer agent for the manufacture of a medicament for the treatment of a cancer in a subject, wherein knowledge of the presence of a RET fusion in said subject has been acquired, and wherein the cancer is chosen from lung cancer, pancreatic cancer, melanoma, colorectal cancer, esophageal-gastric cancer, or adenocarcinoma.

2. The use of claim 1, wherein said anti-cancer agent is a kinase inhibitor.

3. The use of a RET kinase inhibitor for the manufacture of a medicament for the treatment of a cancer associated with a RET fusion, wherein the cancer is chosen from lung cancer, pancreatic cancer, melanoma, colorectal cancer, esophageal-gastric cancer, or adenocarcinoma.

4. The use of any of claims 1-3, wherein said RET fusion is a KIF5B-RET fusion.

5. The use of any of claims 1-4, wherein the anti-cancer agent or the RET kinase inhibitor is a RET-specific inhibitor.

6. The use of any of claims 1-4, wherein the anti-cancer agent or the RET kinase inhibitor is a multi-kinase inhibitor.

7. The use of any of claims 1-4, wherein the anti-cancer agent or the RET kinase inhibitor is chosen from sorafenib (NEXAVAR®), sunitinib (SUTENT®, SU11248), vandetanib (CAPRELSA®, ZD6474), or NVP-AST487.

8. The use of any of claims 1-4, wherein the anti-cancer agent or the RET kinase inhibitor is chosen from:

(i) antisense molecules, ribozymes, RNAi, triple helix molecules that hybridize to a nucleic acid encoding RET, or a transcription regulatory region that blocks or reduces mRNA expression of RET; or

(ii) an anti-cancer agent or RET kinase inhibitor that inhibits the expression of nucleic acid encoding RET.

9. The use of claim 8, wherein the nucleic acid encodes KIF5B-RET, and/or wherein the transcription regulatory region blocks or reduces mRNA expression of KIF5B-RET.

10. The use of any of claims 1-9, wherein the anti-cancer agent or the RET kinase inhibitor is to be administered responsive to the determination of the presence of a RET fusion in a tumor sample from said subject.

11. The use of any of claims 1-10, wherein the medicament is to be administered responsive to acquiring knowledge or information of the presence of the RET fusion in said subject.

12. The use of any of claims 1-11, wherein the medicament is to be administered responsive to acquiring knowledge or information of the presence of the RET fusion in said subject from another party.

13. The use of any of claims 1-12, wherein a communication of the presence of the RET fusion in the subject is received.

14. The use of any of claims 1-13, wherein the medicament is to be administered responsive to an identification of the presence of a KIF5B-RET fusion in the subject.

15. The use of any of claims 1-14, wherein the presence of the RET fusion is determined by sequencing.

16. The use of any of claims 1-15, wherein said cancer is lung cancer.

17. The use of claim 16, wherein said lung cancer is chosen from: small cell lung cancer (SCLC), adenocarcinoma of the lung, bronchogenic carcinoma, non-small cell lung cancer (NSCLC), squamous cell carcinoma (SCC), or a combination thereof.

18. The use of claim 17, wherein the lung cancer is non-small cell lung cancer (NSCLC).

19. The use of claim 17, wherein the lung cancer is squamous cell carcinoma (SCC).

20. The use of claim 7, wherein the anti-cancer agent is sorafenib (NEXAVAR®).

21. The use of claim 7, wherein the anti-cancer agent is sunitinib (SUTENT®, SU11248).

22. The use of claim 7, wherein the anti-cancer agent is vandetanib (CAPRELSA®, ZD6474).

23. The use of claim 7, wherein the anti-cancer agent is NVP-AST487.

24. The use of claim 2, wherein the kinase inhibitor inhibits the expression of nucleic acid encoding KIF5B-RET.

25. The use of claim 2, wherein the kinase inhibitor is selected from antisense molecules, ribozymes, RNAi, triple helix molecules that hybridize to a nucleic acid encoding KIF5B-RET, or a transcription regulatory region that blocks or reduces mRNA expression of KIF5B-RET.

26. The use of any of claims 1-25, wherein the anti-cancer agent or RET kinase inhibitor is administered in combination with a second therapeutic agent or a different therapeutic modality.

27. The use of a kinase inhibitor for the manufacture of a medicament for the treatment of a cancer associated with a RET fusion in a patient, wherein the patient is selected according to the method, comprising:

identifying, selecting, or obtaining information or knowledge that the patient has participated in a clinical trial or has been treated for cancer;

acquiring genotype information that identifies a RET fusion as being in the patient; and

identifying the patient as having an increased risk for, or having, a cancer associated with the RET fusion by detecting the presence of the RET fusion;

wherein the cancer is chosen from lung cancer, pancreatic cancer, melanoma, colorectal cancer, esophageal-gastric cancer, or adenocarcinoma.

28. The use of claim 27, further comprising providing a report to a party.

29. The use of claim 28, wherein the party is the patient, a caregiver, a physician, an oncologist, a hospital, clinic, third-party payor, insurance company or government office.

30. The use of claim 28, wherein said report is in electronic, web-based, or paper form.

31. The use of claim 28, wherein said report identifies the presence or absence of an alteration in a RET nucleic acid sequence, and optionally includes an identifier for the patient from which the sequence was obtained.

32. The use of claim 28, wherein said report comprises;
information on the role of a RET fusion, or wild type sequence, in disease;
information on prognosis, resistance, or potential or suggested therapeutic options;
information on the likely effectiveness of a therapeutic option, the acceptability of a therapeutic option, or the advisability of applying the therapeutic option to a patient; or
information, or a recommendation on, the administration of a drug.

33. A method for generating a personalized cancer treatment report, by obtaining a sample from a subject, detecting a RET fusion in the sample, and selecting a treatment based on the presence or absence of the RET fusion and any other mutation identified.

34. The use of any of claims 27-32, or the method of claim 33, wherein the RET fusion is a KIF5B-RET fusion.

We Claim:

1. Use of an agent that inhibits an activity or expression of KIF5B-RET in the manufacture of a medicament for reducing an activity of a KIF5B-RET fusion, wherein knowledge of the presence of the KIF5B-RET fusion is optionally acquired, and wherein the medicament is to be contacted with the KIF5B-RET fusion, or a KIF5B-RET-expressing cell.

2. The use of claim 1, wherein the contacting step is effected *in vitro*.

3. The use of claim 1, wherein the contacting step is effected in cells in culture.

4. The use of claim 1, wherein the contacting step is effected in a subject.

5. The use of claim 1, wherein the contacting step is effected in an animal subject.

6. Use of an anti cancer agent in the manufacture of a medicament for treating a subject having cancer, wherein knowledge of the presence of a KIF5B-RET fusion in said subject has been acquired.

7. The use of claim 6, wherein said anti cancer agent is a kinase inhibitor.

8. The use of claim 7, wherein the kinase inhibitor is to be administered responsive to the determination of presence of the KIF5B-RET fusion in a tumor sample from said subject.

9. The use of claim 6, wherein the medicament is to be administered responsive to acquiring knowledge or information of the presence of the KIF5B-RET fusion in said subject.

10. The use of claim 6, wherein the medicament is to be administered responsive to acquiring knowledge or information of the presence of the KIF5B-RET fusion in said subject from another party.

11. The use of claim 6, wherein a communication of the presence of the KIF5B-RET fusion in a subject is received.

12. The use of claim 6, wherein the medicament is to be administered responsive to an identification of the presence of the KIF5B-RET fusion in a subject, wherein said identification arises from collaboration with another party.

13. The use of claim 6, wherein the presence of the KIF5B-RET fusion is determined by sequencing.

14. The use of claim 6, wherein said cancer is chosen from pancreatic cancer, melanoma, colorectal cancer, esophageal-gastric cancer, thyroid cancer, or adenocarcinoma.

15. The use of claim 14, wherein said cancer is lung cancer.

16. The use of claim 15, wherein said lung cancer is chosen from: small cell lung cancer (SCLC), adenocarcinoma of the lung, bronchogenic carcinoma, or a combination thereof.

17. The use of claim 15, wherein the lung cancer is non-small cell lung cancer (NSCLC).

18. The use of claim 15, wherein the lung cancer is squamous cell carcinoma (SCC).
19. The use of claim 6, wherein the anti-cancer agent is a multi-kinase inhibitor.
20. The use of claim 6, wherein the anti-cancer agent is a RET-specific inhibitor.
21. The use of claim 6, wherein the anti-cancer agent is sorafenib (NEXAVAR®).
22. The use of claim 6, wherein the anti-cancer agent is sunitinib (SUTENT®, SU11248).
23. The use of claim 6, wherein the anti-cancer agent is vandetanib (CAPRELSA®, ZD6474).
24. The use of claim 6, wherein the anti-cancer agent is NVP-AST487.
25. The use of claim 7, wherein the kinase inhibitor inhibits the expression of nucleic acid encoding KIF5B-RET.
26. The use of claim 7, wherein the kinase inhibitor is selected from antisense molecules, ribozymes, RNAi, triple helix molecules that hybridize to a nucleic acid encoding KIF5B-RET, or a transcription regulatory region that blocks or reduces mRNA expression of KIF5B-RET.
27. The use of claim 7, wherein the kinase inhibitor is administered in combination with a second therapeutic agent or a different therapeutic modality.

28. A method for screening for an agent that modulates, *e.g.*, inhibits, the expression or activity of a KIF5B-RET fusion, comprising:

optionally, determining if a KIF5B-RET fusion is present;
contacting a KIF5B-RET fusion with a candidate agent; and
detecting a change in a parameter associated with a KIF5B-RET fusion.

29. The method of claim 28, wherein said parameter is the expression or an activity of the KIF5B-RET fusion.

30. The method of claim 28, further comprising comparing a value for the parameter to a reference value.

31. The method of claim 28, comprising comparing a parameter obtained from a sample with the candidate agent to a parameter obtained from a sample without the candidate agent.

32. The method of claim 28, further comprising, if a decrease in expression or activity of the KIF5B-RET fusion is detected, identifying or classifying the candidate agent as an inhibitor.

33. The method of claim 28, wherein said contacting occurs in a cell-free system.

34. The method of claim 28, wherein said contacting is effected in a cell in culture.

35. The method of claim 28, wherein said parameter is selected from one or more of:

- (i) direct binding of the candidate agent to a KIF5B-RET fusion polypeptide;
- (ii) a change in kinase activity;
- (iii) a change in an activity of a cell containing a KIF5B-RET fusion, *e.g.*, a change in proliferation, morphology or tumorigenicity of the cell;

(iv) a change in tumor present in an animal subject, *e.g.*, size, appearance, proliferation, of the tumor; or

(v) a change in the level, *e.g.*, expression level, of a KIF5B-RET fusion polypeptide or nucleic acid molecule.

36. A method of determining the presence of a KIF5B-RET fusion comprising:
directly acquiring knowledge that a KIF5B-RET fusion nucleic acid molecule or polypeptide is present in a sample from a subject.

37. The method of claim 36, wherein said sample comprised, fluid, cells, tissue, *e.g.*, a tumor tissue.

38. The method of claim 36, wherein the sample is a nucleic acid sample.

39. The method of claim 36, wherein the sample is a protein sample.

40. The method of claim 36, wherein the sample is acquired from a subject.

41. The method of claim 36, wherein the sample comprises a tumor biopsy or a circulating tumor cell or nucleic acid.

42. The method of claim 36, wherein the tumor is chosen from a colorectal cancer, an esophageal-gastric cancer, a thyroid cancer, an adenocarcinoma or a melanoma.

43. The method of claim 36, wherein the tumor is from a lung cancer.

44. The method of claim 36, wherein the tumor is a NSCLC, a SCLC, a SCC, or a combination thereof.

45. The method of claim 36, wherein the KIF5B-RET fusion is detected in a nucleic acid molecule.

46. The method of claim 45, comprising sequencing by a method chosen from one or more of: nucleic acid hybridization assay, amplification-based assays, PCR-RFLP assay, real-time PCR, sequencing, screening analysis, FISH, spectral karyotyping or MFISH, comparative genomic hybridization), *in situ* hybridization, SSP, HPLC or mass-spectrometric genotyping.

47. The method of claim 36, comprising acquiring a sequence for a position in a nucleic acid molecule by sequencing at least one nucleotide of the nucleic acid molecule, thereby determining that the KIF5B-RET fusion is present in the nucleic acid molecule.

48. The method of claim 47, wherein the sequence acquired is compared to a reference sequence, or a wild type reference sequence.

49. The method of claim 36, wherein a KIF5B-RET fusion polypeptide is detected.

50. The method of claim 36, comprising: contacting a protein sample with a reagent which specifically binds to a KIF5B-RET fusion polypeptide; and detecting the formation of a complex of the KIF5B-RET fusion polypeptide and the reagent.

51. The method of claim 50, wherein the reagent is labeled with a detectable group to facilitate detection of the bound and unbound reagent.

52. The method of claim 50, wherein the reagent is an antibody molecule.

53. The method of claim 36, wherein the level or activity the KIF5B-RET fusion is evaluated.

54. The method of claim 36, wherein the KIF5B-RET fusion is detected prior to initiating, during, or after, a treatment in a subject.

55. The method of claim 36, wherein the KIF5B-RET fusion is detected at the time of diagnosis with a cancer.

56. The method of claim 36, wherein the KIF5B-RET fusion is detected at a pre-determined interval, *e.g.*, a first point in time and at least at a subsequent point in time.

57. The method of claim 36, comprising, responsive to a determination of the presence of the KIF5B-RET fusion, one or more of:

- (1) stratifying a patient population;
- (2) identifying or selecting the subject as likely or unlikely to respond to a treatment;
- (3) selecting a treatment option; or
- (4) prognosticating the time course of the disease in the subject.

58. The method of claim 57, wherein the treatment option comprises administering a kinase inhibitor.

59. The method of claim 57, wherein the kinase inhibitor is sorafenib (NEXAVAR®).

60. The method of claim 57, wherein the kinase inhibitor is sunitinib (SUTENT®, SU11248).

61. The method of claim 57, wherein the kinase inhibitor is vandetanib (ZACTIMA®, ZD6474).

62. The method of claim 57, wherein the kinase inhibitor is NVP-AST487.

63. The method of claim 36, wherein responsive to the direct acquisition of knowledge of the presence of the KIF5B-RET fusion, the subject is classified as a candidate to receive treatment with a kinase inhibitor.

64. The method of claim 36, wherein responsive to the direct acquisition of knowledge of the presence of the KIF5B-RET fusion, the subject, *e.g.*, a patient, can further be assigned to a particular class if a KIF5B-RET fusion is identified in a sample of the patient.

65. The method of claim 36, wherein a patient identified as having a KIF5B-RET fusion can be classified as a candidate to receive treatment with a kinase inhibitor.

66. The method of claim 36, wherein responsive to the direct acquisition of knowledge of presence of the KIF5B-RET fusion, the subject is identified as likely to respond to a treatment that comprises a kinase inhibitor.

67.

Use of a kinase inhibitor in the manufacture of a medicament for treating a cancer associated with the KIF5B-RET fusion in a patient, wherein the patient is selected according to the method, comprising:

identifying, selecting, or obtaining information or knowledge that the patient has participated in a clinical trial or has been treated for cancer;

acquiring genotype information that identifies a KIF5B-RET fusion as being in the patient,

identifying the patient as having an increased risk for, or having, a cancer associated with the KIF5B-RET fusion by detecting the presence of the KIF5B-RET fusion.

68. The use of claim 67, further comprising providing a report to another party.

69. The use of claim 68, wherein the party is the patient, a caregiver, a physician, an oncologist, a hospital, clinic, third-party payor, insurance company or government office.

70. The use of claim 68, wherein said report is in electronic, web-based, or paper form.
71. The use of claim 68, wherein a report is generated which identifies the presence or absence of an alteration described herein, and optionally includes an identifier for the patient from which the sequence was obtained.
72. The use of claim 68, wherein said report comprises;
information on the role of a KIF5B-RET fusion, or wildtype sequence, in disease;
information on prognosis, resistance, or potential or suggested therapeutic options;
information on the likely effectiveness of a therapeutic option, the acceptability of a therapeutic option, or the advisability of applying the therapeutic option to a patient; or
information, or a recommendation on, the administration of a drug.
73. A method for generating a personalized cancer treatment report, by obtaining a sample from a subject, detecting a KIF5B-RET fusion in the sample, and selecting a treatment based on the mutation identified.
74. An isolated or purified nucleic acid molecule that encodes a KIF5B-RET fusion or a breakpoint comprising fragment thereof.
75. An isolated or purified nucleic KIF5B-RET nucleic acid molecule operatively linked to a native or a heterologous regulatory sequence.
76. An isolated or purified vector comprising a nucleic acid molecule that encodes a KIF5B-RET fusion or a breakpoint comprising fragment thereof.
77. A host cell comprising a vector of claim 76.

78. A nucleic acid molecule that specifically reduces or inhibits the expression of a nucleic acid molecule that encodes a KIF5B-RET fusion.

79. The nucleic acid molecule of claim 78, selected from an antisense molecule, ribozyme, siRNA, or triple helix molecule.

80. A nucleic acid molecule suitable as probe, primer, bait or library member that can specifically identify, capture, detect, or isolate, a KIF5B-RET fusion.

81. The nucleic acid of claim 80, wherein said nucleic acid is a probe or primer that includes an oligonucleotide between about 5 and 25 nucleotides in length.

82. The nucleic acid of claim 80, wherein said nucleic acid is a bait that includes an oligonucleotide between about 100 to 300 nucleotides, 130 and 230 nucleotides, or 150 and 200 nucleotides, in length.

83. The nucleic acid of claim 80, wherein said nucleic acid can identify or capture a KIF5B-RET breakpoint, e.g., as identified in FIG. 1.

84. An isolated or purified KIF5B-RET fusion polypeptide or breakpoint containing fragment thereof.

85. The isolated or purified KIF5B-RET fusion polypeptide of claim 84, having a RET kinase activity, and/or a dimerizing or multimerizing activity.

86. An isolated or purified antibody molecule that specifically binds a KIF5B-RET fusion polypeptide.

87. The antibody molecule of claim 86, wherein said antibody molecule is a monospecific antibody molecule.