

NOVEL KIF5B-RET FUSION MOLECULES AND USES THEREOF

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/526,613, filed August 23, 2011; U.S. Provisional Application No. 61/537,024, filed September 20, 2011; U.S. Provisional Application No. 61/542,112, filed September 30, 2011; and U.S. Provisional Application No. 61/594,739, filed February 3, 2012.

BACKGROUND

Cancer represents the phenotypic end-point of multiple genetic lesions that endow cells with a full range of biological properties required for tumorigenesis. Indeed, a hallmark genomic feature of many cancers, including, for example, B cell cancer, lung cancer, breast cancer, ovarian cancer, pancreatic cancer, and colon cancer, is the presence of numerous complex chromosome structural aberrations, including translocations, intra-chromosomal inversions, point mutations, deletions, gene copy number changes, gene expression level changes, and germline mutations, among others.

The need still exists for identifying novel genetic lesions associated with cancer. Such genetic lesions can be an effective approach to develop compositions, methods and assays for evaluating and treating cancer patients.

SUMMARY

The ~~invention~~disclosure is based, at least in part, on the discovery of novel inversion events that include a fragment of a KIF5B gene (“Kinesin Family Member 5B- RET proto-oncogene”) and a fragment of a RET proto-oncogene in a cancer, *e.g.*, a lung cancer, referred to herein as “KIF5B-RET.” The term “KIF5B-RET” or “KIF5B-RET fusion” is used generically herein, and includes any fusion molecule (*e.g.*, gene, gene product (*e.g.*, cDNA, mRNA, or polypeptide), and variant thereof) that includes a fragment of KIF5B and a fragment of RET, including, *e.g.*, a 5’KIF5B-3’RET.

In one embodiment, a KIF5B-RET fusion includes an in-frame fusion of an exon of KIF5B (*e.g.*, one more exons encoding a kinesin motor domain or a fragment thereof)

KIF5B configuration referred to herein as “5’RET-3’KIF5B”). The 5’RET-3’KIF5B configuration of the fusion molecule is not believed to be expressed.

Accordingly, the ~~invention~~disclosure provides, methods of: identifying, assessing or detecting a KIF5B-RET fusion; methods of identifying, assessing, evaluating, and/or treating a subject having a cancer, *e.g.*, a cancer having a KIF5B-RET fusion; isolated KIF5B-RET nucleic acid molecules, nucleic acid constructs, host cells containing the nucleic acid molecules; purified KIF5B-RET polypeptides and binding agents; detection reagents (*e.g.*, probes, primers, antibodies, kits, capable, *e.g.*, of specific detection of a KIF5B-RET nucleic acid or protein); screening assays for identifying molecules that interact with, *e.g.*, inhibit, 5’KIF5B-3’RET fusions, *e.g.*, novel kinase inhibitors; as well as assays and kits for evaluating, identifying, assessing and/or treating a subject having a cancer, *e.g.*, a cancer having a KIF5B-RET fusion. The compositions and methods identified herein can be used, for example, to identify new KIF5B-RET inhibitors; to evaluate, identify or select subject, *e.g.*, a patient, having a cancer; and to treat or prevent a cancer.

KIF5B-RET Nucleic Acid Molecules

In one ~~aspect~~embodiment, the ~~invention~~disclosure features a nucleic acid molecule (*e.g.*, an isolated or purified) nucleic acid molecule that includes a fragment of a KIF5B gene and a fragment of a RET proto-oncogene. In one embodiment, the nucleic acid molecule includes a fusion, *e.g.*, an in-frame fusion, of an exon of KIF5B (*e.g.*, one or more exons encoding a kinesin motor domain or a fragment thereof), and an exon of RET (*e.g.*, one or more exons encoding a RET tyrosine kinase domain or a fragment thereof).

In an embodiment the 5’KIF5B-3’RET nucleic acid molecule comprises sufficient KIF5B and sufficient RET sequence such that the encoded 5’KIF5B-3’RET fusion has kinase activity, *e.g.*, has elevated activity, *e.g.*, kinase activity, as compared with wild type RET, *e.g.*, in a cell of a cancer referred to herein. In an embodiment the encoded 5’KIF5B-3’RET fusion comprises at least 1, 2, 3, 4, 5, 6, 7, 9, 10, or 11 exons from KIF5B and at least 1, 2, 3, 4, 5, 6, 7, 9, or 10, RET exons. In one embodiment, the encoded 5’KIF5B-3’RET fusion polypeptide includes a kinesin motor domain, a coiled coil domain, or a functional fragment thereof, and a RET tyrosine kinase domain or a functional fragment thereof.

embodiments, the KIF5B-RET fusion is in a 5'-RET to 3'-KIF5B configuration referred to herein as "5'RET-3'KIF5B"). In one embodiment, the nucleic acid molecule includes the nucleotides sequence of 1-2136 of SEQ ID NO:3 (corresponding to exons 1-11 of a RET gene) or a fragment thereof, or a sequence substantially identical thereto. In another embodiment, the nucleic acid molecule includes the nucleotides sequence of 2137-3360 of SEQ ID NO:3 (corresponding to exons 16-25 of the a KIF5B gene) or a fragment thereof, or a sequence substantially identical thereto. In yet other embodiments, the nucleic acid molecule includes the nucleotide sequence shown in FIGs. 4A-4D (*e.g.*, SEQ ID NO:3) or a fragment thereof, or a sequence substantially identical thereto. In one embodiment, the nucleic acid molecule is complementary to at least a portion of a nucleotide sequence disclosed herein, *e.g.*, is capable of hybridizing under a stringency condition described herein to SEQ ID NO:3 or a fragment thereof. In yet other embodiment, the nucleic acid molecule hybridizes to a nucleotide sequence that is complementary to at least a portion of a nucleotide sequence disclosed herein, *e.g.*, is capable of hybridizing under a stringency condition to a nucleotide sequence complementary to SEQ ID NO:3 or a fragment thereof. The nucleotide sequence of a cDNA encoding an exemplary 5'RET-3'KIF5B fusion is shown in SEQ ID NO:3, and the predicted amino acid sequence is shown in SEQ ID NO:4. RT-PCR studies have shown that the RET exon 11 and KIF5B exon 16 did not yield a transcription product.

In a related ~~aspect~~embodiment, the ~~invention~~disclosure features nucleic acid constructs that include the KIF5B-RET nucleic acid molecules described herein. In certain embodiments, the nucleic acid molecules are operatively linked to a native or a heterologous regulatory sequence. Also included are vectors and host cells that include the KIF5B-RET nucleic acid molecules described herein, *e.g.*, vectors and host cells suitable for producing the nucleic acid molecules and polypeptides described herein.

In a related ~~aspect~~embodiment, methods of producing the nucleic acid molecules and polypeptides described herein are also described.

In another ~~aspect~~embodiment, the ~~invention~~disclosure features nucleic acid molecules that reduces or inhibits the expression of a nucleic acid molecule that encodes a KIF5B-RET fusion described herein. Examples of such nucleic acid molecules include, for example, antisense molecules, ribozymes, RNAi, triple helix molecules that hybridize to a nucleic

acid encoding KIF5B-RET, or a transcription regulatory region of KIF5B-RET, and blocks or reduces mRNA expression of KIF5B-RET.

Nucleic Acid Detection and Capturing Reagents

5 | The ~~invention~~disclosure also features a nucleic acid molecule, *e.g.*, nucleic acid fragment, suitable as probe, primer, bait or library member that includes, flanks, hybridizes to, which are useful for identifying, or are otherwise based on, the KIF5B-RET fusions described herein. In certain embodiments, the probe, primer or bait molecule is an oligonucleotide that allows capture, detection or isolation of a KIF5B-RET fusion nucleic acid molecule described herein. The oligonucleotide can comprise a nucleotide sequence substantially complementary to a fragment of the KIF5B-RET fusion nucleic acid molecules described herein. The sequence identity between the nucleic acid fragment, *e.g.*, the oligonucleotide, and the target KIF5B-RET sequence need not be exact, so long as the sequences are sufficiently complementary to allow the capture, detection or isolation of the target sequence. In one embodiment, the nucleic acid fragment is a probe or primer that includes an oligonucleotide between about 5 and 25, *e.g.*, between 10 and 20, or 10 and 15 nucleotides in length. In other embodiments, the nucleic acid fragment is a bait that includes an oligonucleotide between about 100 to 300 nucleotides, 130 and 230 nucleotides, or 150 and 200 nucleotides, in length.

20 | In one embodiment, the nucleic acid fragment can be used to identify or capture, *e.g.*, by hybridization, a KIF5B-RET fusion. For example, the nucleic acid fragment can be a probe, a primer, or a bait, for use in identifying or capturing, *e.g.*, by hybridization, a KIF5B-RET fusion described herein. In one embodiment, the nucleic acid fragment can be useful for identifying or capturing a KIF5B-RET breakpoint, *e.g.*, as identified in FIG.

25 | 1. In one embodiment, the nucleic acid fragment hybridizes to a nucleotide sequence within a chromosomal rearrangement that creates an in-frame fusion of exon 15 of KIF5B with exon 12 of RET (*e.g.*, a sequence within an 11MB pericentric inversion on chromosome 10). In one embodiment, the nucleic acid fragment hybridizes to a nucleotide sequence in the region of 32,316,376-32,316,416 of chromosome 10 coupled to (*e.g.*, juxtaposed to) nucleotides in the region of nucleotides 43,611,042-43,611,118 of chromosome 10. In one embodiment, the nucleic acid fragment hybridizes to a nucleotide sequence that includes a breakpoint, *e.g.*, a breakpoint as identified in FIGs. 1,

In other embodiments, the nucleic acid fragment includes a library member comprising a KIF5B-RET nucleic acid molecule described herein. In one embodiment, the library member includes a rearrangement that results in a KIF5B-RET fusion described herein.

5 The nucleic acid fragment can be detectably labeled with, *e.g.*, a radiolabel, a fluorescent label, a bioluminescent label, a chemiluminescent label, an enzyme label, a binding pair label, or can include an affinity tag; a tag, or identifier (*e.g.*, an adaptor, barcode or other sequence identifier).

10 KIF5B-RET Fusion Polypeptides

In another ~~aspect~~embodiment, the ~~invention~~disclosure features a KIF5B-RET fusion polypeptide (*e.g.*, a purified KIF5B-RET fusion polypeptide), a biologically active or antigenic fragment thereof, as well as reagents (*e.g.*, antibody molecules that bind to a KIF5B-RET fusion polypeptide), methods for modulating a KIF5B-RET
15 polypeptide activity and detection of a KIF5B-RET polypeptide.

In one embodiment, the KIF5B-RET fusion polypeptide has at least one biological activity, *e.g.*, a RET kinase activity, and/or a dimerizing or multimerizing activity. In one embodiment, at least one biological activity of the KIF5B-RET fusion polypeptide is reduced or inhibited by an anti-cancer drug, *e.g.*, a kinase inhibitor
20 (*e.g.*, a multikinase inhibitor or a RET-specific inhibitor). In one embodiment, at least one biological activity of the KIF5B-RET fusion polypeptide is reduced or inhibited by a kinase inhibitor chosen from lenvatinib (E7080), sorafenib (NEXAVAR®), sunitinib (SUTENT®, SU11248), vandetanib (CAPRELSA®, ZACTIMA®, ZD6474), NVP-AST487, regorafenib (BAY-73-4506), motesanib (AMG 706),
25 cabozantinib (XL-184), apatinib (YN-968D1), or DCC-2157.

In other embodiments, the KIF5B-RET fusion polypeptide includes a fragment of a KIF5B polypeptide and a fragment of a RET polypeptide. In one embodiment, the KIF5B-RET fusion polypeptide includes amino acids 578-575 of SEQ ID NO:2 or a fragment thereof (*e.g.*, amino acids 1-575 of SEQ ID NO:2 or a fragment thereof), and
30 amino acids 576-624 of SEQ ID NO:2 or a fragment thereof (*e.g.*, amino acids 576-977 of SEQ ID NO:2 or a fragment thereof). In yet other embodiments, the KIF5B-RET fusion polypeptide includes an amino acid sequence substantially identical to an in-frame

junction between the RET transcript and the KIF5B transcript, *e.g.*, a nucleotide sequence within SEQ ID NO:3 (*e.g.*, a sequence comprising nucleotides 2131-2142, 2128-2145, or 2125-2148 of SEQ ID NO:3 (see FIG. 4B)). In yet other embodiments, the KIF5B-RET fusion polypeptide is encoded by the nucleotide sequence shown in FIGs. 4A-4D (*e.g.*,
5 SEQ ID NO:3) or a fragment thereof, or a sequence substantially identical thereto.

In an embodiment, the 5'KIF5B-3'RET fusion polypeptide comprises sufficient KIF5B and sufficient RET sequence such that it has kinase activity, *e.g.*, has elevated activity, *e.g.*, kinase activity, as compared with wild type RET, *e.g.*, in a cell of a cancer referred to herein. In an embodiment the 5'KIF5B-3'RET fusion polypeptide comprises
10 at least 1, 2, 3, 4, 5, 6, 7, 9, 10, or 11 exons from KIF5B and at least 1, 2, 3, 4, 5, 6, 7, 9, or 10, RET exons. In one embodiment, the 5'KIF5B-3'RET fusion polypeptide includes a kinesin motor domain or a functional fragment thereof, and a RET tyrosine kinase domain or a functional fragment thereof. In a related ~~aspectembodiment~~, the ~~inventiondisclosure~~ features KIF5B-RET fusion polypeptide or fragments operatively
15 linked to heterologous polypeptides to form fusion proteins.

In another embodiment, the KIF5B-RET fusion polypeptide or fragment is a peptide, *e.g.*, an immunogenic peptide or protein, that contains a fusion junction described herein. Such immunogenic peptides or proteins can be used to raise antibodies specific to the fusion protein. In other embodiments, such immunogenic peptides or
20 proteins can be used for vaccine preparation. The vaccine preparation can include other components, *e.g.*, an adjuvant.

In another ~~aspectembodiment~~, the ~~inventiondisclosure~~ features antibody molecules that bind to a KIF5B-RET fusion polypeptide or fragment described herein. In embodiments the antibody can distinguish wild type RET (or KIF5B) from KIF5B-RET.
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Methods Reducing a KIF5B-RET Activity

In another ~~aspectembodiment~~, the ~~inventiondisclosure~~ features a method of reducing an activity of a KIF5B-RET fusion. The method includes contacting the KIF5B-RET fusion, or a KIF5B-RET-expressing cell, with an agent that inhibits an
30 activity or expression of KIF5B-RET (*e.g.*, a kinase inhibitor). In one embodiment, the contacting step can be effected *in vitro*, *e.g.*, in a cell lysate or in a reconstituted system. Alternatively, the method can be performed on cells in culture, *e.g.*, *in vitro* or *ex vivo*. In other

embodiments, the method can be performed on KIF5B-RET-expressing cells present in a subject, *e.g.*, as part of an *in vivo* (*e.g.*, therapeutic or prophylactic) protocol. In an embodiment the method is practiced on an animal subject (*e.g.*, an *in vivo* animal model). In certain embodiments, the KIF5B-RET fusion is a nucleic acid molecule or a polypeptide as described herein.

In one aspect, there is provided the use of a RET kinase inhibitor for the manufacture of a medicament for the treatment of a cancer in a subject, wherein the RET kinase inhibitor is to be administered responsive to a determination of a presence of a Kinesin Family Member 5B (KIF5B)-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in said cancer, wherein the cancer is a lung cancer or a colorectal cancer, wherein the RET kinase inhibitor is chosen from cabozantinib, lenvatinib, or vandetanib.

In a related aspect/embodiment, a method of inhibiting, reducing, or treating a hyperproliferative disorder, *e.g.*, a cancer, in a subject is provided. The method includes administering to the subject a preselected therapeutic agent, *e.g.*, an anti-cancer agent (*e.g.*, a kinase inhibitor), as a single agent, or in combination, in an amount sufficient to reduce, inhibit or treat the activity or expression of KIF5B-RET (*e.g.*, a KIF5B-RET fusion described herein), thereby inhibiting, reducing, or treating the hyperproliferative disorder in the subject. "Treatment" as used herein includes, but is not limited to, inhibiting tumor growth, reducing tumor mass, reducing size or number of metastatic lesions, inhibiting the development of new metastatic lesions, prolonged survival, prolonged progression-free survival, prolonged time to progression, and/or enhanced quality of life.

In one aspect, there is provided the use of a RET kinase inhibitor for the manufacture of a medicament for the treatment of a cancer associated with a KIF5B-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a patient, wherein the patient is selected according to a method, comprising:

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

acquiring genotype information that identifies the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide as being in the patient,

identifying the patient as having an increased risk for, or having, the cancer associated with the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide by detecting a presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide,
5 wherein the cancer is a lung cancer or a colorectal cancer, and wherein the RET kinase inhibitor is chosen from cabozantinib, lenvatinib, or vandetanib.

In one embodiment, the kinase inhibitor is administered based on a determination that a KIF5B-RET fusion is present in a subject, e.g., based on its present in a subject's sample. Thus, treatment can be combined with a KIF5B-RET
10 detection or evaluation method, e.g., as described herein, or administered in response to a determination made by a KIF5B-RET detection or evaluation method, e.g., as described herein. In certain embodiments, the kinase inhibitor is administered responsive to acquiring knowledge or information of the presence of the KIF5B-RET fusion in a subject. In one embodiment, the kinase inhibitor is administered
15 responsive to acquiring knowledge or information on the subject's genotype, e.g., acquiring knowledge or information that the patient's genotype has a KIF5B-RET fusion. In other embodiments, the kinase inhibitor is administered responsive to receiving a communication (e.g., a report) of the presence of the KIF5B-RET fusion in a subject (e.g., a subject's sample). In yet other embodiments, the kinase inhibitor
20 is administered responsive to information obtained from a collaboration with another party that identifies the presence of the KIF5B-RET fusion in a subject (e.g., a subject's sample). In other embodiments, the kinase inhibitor is administered

Screening Methods

In another aspect embodiment, the invention disclosure features a method, or assay, for screening for agents that modulate, *e.g.*, inhibit, the expression or activity of a KIF5B-RET fusion, *e.g.*, a KIF5B-RET fusion as described herein. The method includes contacting a KIF5B-RET fusion, or a cell expressing a KIF5B-RET fusion, with a candidate agent; and detecting a change in a parameter associated with a KIF5B-RET fusion, *e.g.*, a change in the expression or an activity of the KIF5B-RET fusion. The method can, optionally, include comparing the treated parameter to a reference value, *e.g.*, a control sample (*e.g.*, comparing a parameter obtained from a sample with the candidate agent to a parameter obtained from a sample without the candidate agent). In one embodiment, if a decrease in expression or activity of the KIF5B-RET fusion is detected, the candidate agent is identified as an inhibitor. In another embodiment, if an increase in expression or activity of the KIF5B-RET fusion is detected, the candidate agent is identified as an activator. In certain embodiments, the KIF5B-RET fusion is a nucleic acid molecule or a polypeptide as described herein.

In one embodiment, the contacting step is effected in a cell-free system, *e.g.*, a cell lysate or in a reconstituted system. In other embodiments, the contacting step is effected in a cell in culture, *e.g.*, a cell expressing a KIF5B-RET fusion (*e.g.*, a mammalian cell, a tumor cell or cell line, a recombinant cell). In yet other embodiments, the contacting step is effected in a cell *in vivo* (a KIF5B-RET-expressing cell present in a subject, *e.g.*, an animal subject (*e.g.*, an *in vivo* animal model).

Exemplary parameters evaluated include one or more of:

(i) a change in binding activity, *e.g.*, direct binding of the candidate agent to a KIF5B-RET fusion polypeptide; a binding competition between a known ligand and the candidate agent to a KIF5B-RET fusion polypeptide;

(ii) a change in kinase activity, *e.g.*, phosphorylation levels of a KIF5B-RET fusion polypeptide (*e.g.*, an increased or decreased autophosphorylation); or a change in phosphorylation of a target of a RET kinase, *e.g.*, focal adhesion kinase (FAK), persephin or glial derived neurotrophic factor (GDNF). In certain embodiments, a change in kinase activity, *e.g.*, phosphorylation, is detected by any of Western blot (*e.g.*, using an anti-KIF5B or anti-RET antibody; a phosphor-specific antibody, detecting a shift in the

administered to the animal subject and a change in the tumor is detected. In one embodiment, the change in the tumor includes one or more of a tumor growth, tumor size, tumor burden, survival, is evaluated. A decrease in one or more of tumor growth, tumor size, tumor burden, or an increased survival is indicative that the candidate agent is an inhibitor.

In other embodiments, a change in expression of a KIF5B-RET fusion can be monitored by detecting the nucleic acid or protein levels, *e.g.*, using the methods described herein.

In certain embodiments, the screening methods described herein can be repeated and/or combined. In one embodiment, a candidate agent that is evaluated in a cell-free or cell-based described herein can be further tested in an animal subject.

In one embodiment, the candidate agent is a small molecule compound, *e.g.*, a kinase inhibitor, a nucleic acid (*e.g.*, antisense, siRNA, aptamer, ribozymes, microRNA), an antibody molecule (*e.g.*, a full antibody or antigen binding fragment thereof that binds to KIF5B5 or RET). The candidate agent can be obtained from a library (*e.g.*, a commercial library of kinase inhibitors) or rationally designed (*e.g.*, based on the RET kinase domain).

Methods for Detecting KIF5B-RET Fusions

In another aspect, ~~embodiment~~, the ~~invention~~ disclosure features a method of determining the presence of a KIF5B-RET fusion, *e.g.*, a KIF5B-RET fusion as described herein. In one embodiment, the KIF5B-RET fusion is detected in a nucleic acid molecule or a polypeptide. The method includes detecting whether a KIF5B-RET fusion nucleic acid molecule or polypeptide is present in a cell (*e.g.*, a circulating cell), a tissue (*e.g.*, a tumor), or a sample, *e.g.*, a tumor sample, from a subject. In one embodiment, the sample is a nucleic acid sample. In one embodiment, the nucleic acid sample comprises DNA, *e.g.*, genomic DNA or cDNA, or RNA, *e.g.*, mRNA. In other embodiments, the sample is a protein sample.

In one embodiment, the sample is, or has been, classified as non-malignant using other diagnostic techniques, *e.g.*, immunohistochemistry.

In one embodiment, the sample is acquired from a subject (*e.g.*, a subject having or at risk of having a cancer, *e.g.*, a patient), or alternatively, the method further includes

acquiring a sample from the subject. The sample can be chosen from one or more of: tissue, e.g., cancerous tissue (e.g., a tissue biopsy), whole blood, serum, plasma, buccal scrape, sputum, saliva, cerebrospinal fluid, urine, stool, circulating tumor cells, circulating nucleic acids, or bone marrow. In certain embodiments, the sample is a tissue (e.g., a tumor biopsy), a circulating tumor cell or nucleic acid.

In embodiments, the tumor is from a cancer described herein, e.g., is chosen from a lung cancer, a colorectal cancer, an esophageal-gastric cancer, a thyroid cancer, an adenocarcinoma or a melanoma. In one embodiment, the tumor is from a lung cancer, e.g., a NSCLC, a SCLC, a SCC, or a combination thereof.

In one embodiment, the subject is at risk of having, or has a cancer (e.g., a patient with a cancer described herein). For example, in one embodiment, the subject is at risk for having, or has a lung cancer.

In other embodiments, the KIF5B-RET fusion is detected in a nucleic acid molecule by a method chosen from one or more of: nucleic acid hybridization assay, amplification-based assays (e.g., polymerase chain reaction (PCR)), PCR-RFLP assay, real-time PCR, sequencing, screening analysis (including metaphase cytogenetic analysis by standard karyotype methods, FISH (e.g., break away FISH), spectral karyotyping or MFISH, comparative genomic hybridization), *in situ* hybridization, SSP, HPLC or mass-spectrometric genotyping.

In one embodiment, the method includes: contacting a nucleic acid sample, e.g., a genomic DNA sample (e.g., a chromosomal sample or a fractionated, enriched or otherwise pre-treated sample) or a gene product (mRNA, cDNA), obtained from the subject, with a nucleic acid fragment (e.g., a probe or primer as described herein (e.g., an exon-specific probe or primer) under conditions suitable for hybridization, and determining the presence or absence of the KIF5B-RET nucleic acid molecule. The method can, optionally, include enriching a sample for the gene or gene product.

In a related aspect/embodiment, a method for determining the presence of a KIF5B-RET fusion nucleic acid molecule is provided. The method includes: acquiring a sequence for a position in a nucleic acid molecule, e.g., by sequencing at least one nucleotide of the nucleic acid molecule (e.g., sequencing at least one nucleotide in the nucleic acid molecule that comprises the KIF5B-RET fusion), thereby determining that the KIF5B-RET fusion is present in the nucleic acid molecule. Optionally, the sequence acquired is

compared to a reference sequence, or a wild type reference sequence. In one embodiment, the nucleic acid molecule is from a cell (*e.g.*, a circulating cell), a tissue (*e.g.*, a tumor), or any sample from a subject (*e.g.*, blood or plasma sample). In other embodiments, the nucleic acid molecule from a tumor sample (*e.g.*, a tumor or cancer sample) is sequenced. In one embodiment, the sequence is determined by a next generation sequencing method. The method further can further include acquiring, *e.g.*, directly or indirectly acquiring, a sample, *e.g.*, a tumor or cancer sample, from a subject (*e.g.*, a patient). In certain embodiments, the cancer is chosen from a lung cancer, colorectal cancer, esophageal-gastric cancer or melanoma.

In another aspect embodiment, the invention disclosure features a method of analyzing a tumor or a circulating tumor cell. The method includes acquiring a nucleic acid sample from the tumor or the circulating cell; and sequencing, *e.g.*, by a next generation sequencing method, a nucleic acid molecule, *e.g.*, a nucleic acid molecule that includes a KIF5B-RET fusion described herein.

In yet another embodiment, a KIF5B-RET fusion polypeptide is detected. The method includes: 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. In one embodiment, the reagent is labeled with a detectable group to facilitate detection of the bound and unbound reagent. In one embodiment, the reagent is an antibody molecule, *e.g.*, is selected from the group consisting of an antibody, and antibody derivative, and an antibody fragment.

In yet another embodiment, the level (*e.g.*, expression level) or activity the KIF5B-RET fusion is evaluated. For example, the level (*e.g.*, expression level) or activity of the KIF5B-RET fusion (*e.g.*, mRNA or polypeptide) is detected and (optionally) compared to a pre-determined value, *e.g.*, a reference value (*e.g.*, a control sample).

In yet another embodiment, the KIF5B-RET fusion is detected prior to initiating, during, or after, a treatment in a subject, *e.g.*, a treatment with a kinase inhibitor. In one embodiment, the KIF5B-RET fusion is detected at the time of diagnosis with a cancer. In other embodiment, 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.

In yet another embodiment, responsive to the determination of the presence of the KIF5B-RET fusion, the method includes administering a kinase inhibitor, *e.g.*, a kinase inhibitor as described herein, to the subject.

5 Method of Evaluating a Tumor or a Subject

 In another aspect ~~embodiment~~, the ~~invention~~ disclosure features a method of evaluating a subject (*e.g.*, a patient), *e.g.*, for risk of having or developing a cancer, *e.g.*, a lung cancer, colorectal cancer or skin cancer. The method includes: acquiring information or knowledge of the presence of a KIF5B-RET fusion in a subject (*e.g.*,
10 acquiring genotype information of the subject that identifies a KIF5B-RET fusion as being present in the subject); acquiring a sequence for a nucleic acid molecule identified herein (*e.g.*, a nucleic acid molecule that includes a KIF5B-RET fusion sequence); or detecting the presence of a KIF5B-RET fusion nucleic acid or polypeptide in the subject), wherein the presence of the KIF5B-RET fusion is positively correlated with increased
15 risk for, or having, a cancer associated with the KIF5B-RET fusion.

 The method can further include the step(s) of identifying (*e.g.*, evaluating, diagnosing, screening, and/or selecting) the subject as being positively correlated with increased risk for, or having, a cancer associated with the KIF5B-RET fusion. In one embodiment, the subject is identified or selected as likely or unlikely to respond to a
20 treatment, *e.g.*, a kinase inhibitor treatment as described herein.

 The method can further include treating the subject with a kinase inhibitor, *e.g.*, a kinase inhibitor as described herein.

 The method can further include acquiring, *e.g.*, directly or indirectly, a sample from a patient and evaluating the sample for the present of a KIF5B-RET fusion as
25 described herein.

 In certain embodiments, the subject is a patient or patient population that has participated in a clinical trial. In one embodiment, the subject has participated in a clinical trial for evaluating a kinase inhibitor (*e.g.*, a multikinase inhibitor or a RET inhibitor). In one embodiment, the clinical trial is discontinued or terminated. In other
30 embodiments, the subject has participated in a clinical trial that evaluates a RET kinase, a KIF5B inhibitor (*e.g.*, a kinesin inhibitor), an upstream or downstream component of RET or KIF5B. In one embodiment, the subject responded favorably to the clinical trial,

e.g., experience an improvement in at least one symptom of a cancer (*e.g.*, decreased in tumor size, rate of tumor growth, increased survival). In other embodiments, the subject did not respond in a detectable way to the clinical trial.

In a related ~~aspect~~embodiment, a method of evaluating a patient or a patient population is provided. The method includes: identifying, selecting, or obtaining information or knowledge that the patient or patient population has participated in a clinical trial;

acquiring information or knowledge of the presence of a KIF5B-RET fusion in the patient or patient population (*e.g.*, acquiring genotype information of the subject that identifies a KIF5B-RET fusion as being present in the subject); acquiring a sequence for a nucleic acid molecule identified herein (*e.g.*, a nucleic acid molecule that includes a KIF5B-RET fusion sequence); or detecting the presence of a KIF5B-RET fusion nucleic acid or polypeptide in the subject), wherein the presence of the KIF5B-RET fusion identifies the patient or patient population as having an increased risk for, or having, a cancer associated with the KIF5B-RET fusion.

In certain embodiments, the subject is a patient or patient population that has participated in a clinical trial. In one embodiment, the subject has participated in a clinical trial for evaluating a kinase inhibitor (*e.g.*, a multikinase inhibitor or a RET inhibitor). In one embodiment, the clinical trial is discontinued or terminated. In other embodiments, the subject has participated in a clinical trial that evaluates a RET kinase, a KIF5B inhibitor (*e.g.*, a kinesin inhibitor), an upstream or downstream component of RET or KIF5B. In one embodiment, the subject responded favorably to the clinical trial, *e.g.*, experience an improvement in at least one symptom of a cancer (*e.g.*, decreased in tumor size, rate of tumor growth, increased survival). In other embodiments, the subject did not respond in a detectable way to the clinical trial.

In embodiments, the method further includes treating the subject with a kinase inhibitor, *e.g.*, a kinase inhibitor as described herein.

Reporting

Methods described herein can include providing a report, such as, in electronic, web-based, or paper form, to the patient or to another person or entity, *e.g.*, a caregiver, *e.g.*, a physician, *e.g.*, an oncologist, a hospital, clinic, third-party payor, insurance company or government office. The report can include output from the method, *e.g.*, the

identification of nucleotide values, the indication of presence or absence of a KIF5B-RET fusion as described herein, or wildtype sequence. In one embodiment, a report is generated, such as in paper or electronic form, 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.

The report can also include information on the role of a sequence, *e.g.*, a KIF5B-RET fusion as described herein, or wildtype sequence, in disease. Such information can include information on prognosis, resistance, or potential or suggested therapeutic options. The report can include 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, *e.g.*, a patient having a sequence, alteration or mutation identified in the test, and in embodiments, identified in the report. For example, the report can include information, or a recommendation on, the administration of a drug, *e.g.*, the administration at a preselected dosage or in a preselected treatment regimen, *e.g.*, in combination with other drugs, to the patient. In an embodiment, not all mutations identified in the method are identified in the report. For example, the report can be limited to mutations in genes having a preselected level of correlation with the occurrence, prognosis, stage, or susceptibility of the cancer to treatment, *e.g.*, with a preselected therapeutic option. The report can be delivered, *e.g.*, to an entity described herein, within 7, 14, or 21 days from receipt of the sample by the entity practicing the method.

In one aspect, there is provided a method for generating a personalized cancer treatment report, by detecting a KIF5B-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a tumor sample from a patient, and selecting a RET kinase inhibitor for the patient based on an identification of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in the tumor sample, wherein the cancer is a lung cancer or a colorectal cancer, and wherein the RET kinase inhibitor is chosen from cabozantinib, lenvatinib, or vandetanib.

In another ~~aspect~~embodiment, the ~~invention~~disclosure features a method for generating a report, *e.g.*, a personalized cancer treatment report, by obtaining a sample, *e.g.*, a tumor sample, from a subject, detecting a KIF5B-RET fusion as described herein in the sample, and selecting a treatment based on the mutation identified. In one
5 embodiment, a report is generated that annotates the selected treatment, or that lists, *e.g.*, in order of preference, two or more treatment options based on the mutation identified. In another embodiment, the subject, *e.g.*, a patient, is further administered the selected method of treatment.

Unless otherwise defined, all technical and scientific terms used herein have the
10 same meaning as commonly understood by one of ordinary skill in the art to which this ~~invention~~disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the ~~invention~~disclosure, suitable methods

and materials are described below. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and the example are illustrative only and not intended to be limiting.

The details of one or more embodiments featured in the ~~invention~~disclosure are set forth in the accompanying drawings and the description below. Other features, objects, and advantages featured in the ~~invention~~disclosure will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a snapshot of the sequencing reads illustrating that there are RET read pairs that map on one end to 5'KIF5B and on the other end to 3'RET, and other RET read pairs that map on one end to 5'RET and on the other end to 3'KIFB.

FIGs. 2A and 2B are schematic diagrams illustrating the inversion event that brings together exon 15 of KIF5B and exon 12 of RET. FIGs 2A and 2B disclose SEQ ID NOS 6 and 7, respectively.

FIGs. 3A to 3D are the predicted cDNA sequence (SEQ ID NO:1) and protein sequence of the KIF5B-RET fusion (SEQ ID NO:2). The KIF5B portion of the cDNA sequence is equivalent to nucleotides 471-2195 of RefSeq NM_004521.2, and the KIF5B portion of the protein sequence is equivalent to amino acids 1-575 of RefSeq NP_004512. The KIF5B portions of the cDNA and protein sequences are underlined. The RET portion of the cDNA sequence is equivalent to nucleotides 2327-3535 of RefSeq NM_020975, and the RET portion of the protein sequence is equivalent to amino acids 713-1114 of RefSeq NP_066124.1. The intact tyrosine kinase domain of RET is represented by a gray box (see FIG. 3C).

FIGs. 4A to 4D are the predicted cDNA sequence (SEQ ID NO:3) and protein sequence of the RET-KIF5B fusion (SEQ ID NO:4). The cDNA sequence of the RET portion of the fusion transcript is equivalent to nucleotides 190-2326 of RefSeq NM_020975, and the protein sequence is equivalent to amino acids 1-712 of RefSeq NP_066124.1. The cDNA sequence of the KIF5B portion of the fusion transcript is equivalent to nucleotides 2196-3362 of RefSeq NM_004521.2, and the protein portion is equivalent to amino acids 576-963 of RefSeq NP_004512. The KIF5B portions of the cDNA and protein sequences are underlined.

We Claim:

1. Use of a RET kinase inhibitor for the manufacture of a medicament for the treatment of a cancer in a subject, wherein the RET kinase inhibitor is to be administered responsive to a determination of a presence of a Kinesin Family Member 5B (KIF5B)-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in said cancer, and wherein the cancer is chosen from a lung cancer, a pancreatic cancer, a melanoma, a colorectal cancer, an esophageal-gastric cancer, or an adenocarcinoma.

2. Use of a RET kinase inhibitor for the manufacture of a medicament for the treatment of a cancer in a subject, wherein the RET kinase inhibitor is to be administered responsive to a determination of a presence of a KIF5B-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in said cancer, and wherein the kinase inhibitor is chosen from cabozantinib, lenvatinib, vandetanib, sorafenib, sunitinib, NVP-AST487, regorafenib, motesanib, apatinib, or DCC-2157.

3. The use of claim 1 or 2, wherein the RET-kinase inhibitor is a RET-specific inhibitor.

4. The use of claim 1 or 2, wherein the RET kinase inhibitor is a multi-kinase inhibitor that inhibits the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide.

5. The use of any of claims 1 or 4, wherein the RET kinase inhibitor is chosen from cabozantinib, lenvatinib, vandetanib, sorafenib, sunitinib, NVP-AST487, regorafenib, motesanib, apatinib, or DCC-2157.

6. The use of any of claims 1, 3 or 4, wherein the RET kinase inhibitor is chosen from:
(i) an antisense molecule, a ribozyme, an RNAi molecule, or a triple helix molecules that hybridizes to the nucleic acid molecule encoding the KIF5B-RET polypeptide, or a transcription regulatory region that blocks or reduces mRNA expression of the nucleic acid molecule encoding the KIF5B-RET polypeptide; or

(ii) an RET kinase inhibitor that inhibits the expression of the nucleic acid encoding the KIF5B-RET polypeptide.

7. The use of any of claims 1-6, wherein the RET kinase inhibitor is to be administered responsive to the determination of the presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a tumor sample from said subject.

8. The use of claim 7, wherein the tumor sample:

- (i) comprises fluid, cells, and/or a tissue;
- (ii) is a nucleic acid sample or a protein sample; and/or
- (iii) comprises a tumor biopsy or a circulating tumor cell or nucleic acid.

9. The use of any of claims 1-8, wherein:

- (i) the level or activity of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is evaluated;
- (ii) the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is detected prior to initiating, during, or after, the treatment in the subject;
- (iii) the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is detected at the time of diagnosis of the subject with the cancer; and/or
- (iv) the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is detected at a pre-determined interval.

10. The use of any of claims 1-9, wherein the determination of the presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide comprises acquiring knowledge or information of the presence of the KIF5B-RET polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in said subject from another party.

11. The use of any of claims 1-10, wherein a communication of the presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a subject is received.

12. The use of any of claims 1-11, wherein the presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is determined by a method chosen from one or more of: a nucleic acid hybridization assay, an amplification-based assay, a PCT-RFLP assay, real-time PCR, sequencing, a screening analysis, FISH, spectral karyotyping or MFISH, comparative genomic hybridization, *in situ* hybridization, SSP, HPLC, or mass-spectrometric genotyping.

13. The use of any of claims 1-12, wherein said cancer is a lung cancer.

14. The use of claim 13, wherein said lung cancer is chosen from: a small cell lung cancer (SCLC), an adenocarcinoma of the lung, a bronchogenic carcinoma, a non-small cell lung cancer (NSCLC), a squamous cell carcinoma (SCC), or a combination thereof.

15. The use of claim 13 or 14, wherein the lung cancer is a non-small cell lung cancer (NSCLC).

16. The use of claim 13 or 14, wherein the lung cancer is a squamous cell carcinoma (SCC).

17. The use of any of claims 1-12, wherein the cancer is a colon cancer.

18. The use of any of claims 1, 2 or 4-17, wherein the RET kinase inhibitor is cabozantinib.

19. The use of any of claims 1, 2 or 4-17, wherein the RET kinase inhibitor is lenvatinib.

20. The use of any of claims 1, 2 or 4-17, wherein the RET kinase inhibitor is vandetanib.

21. The use of any of claims 1-20, wherein the RET kinase inhibitor is administered in combination with a second therapeutic agent or a different therapeutic modality.

22. Use of a RET kinase inhibitor for the manufacture of a medicament for the treatment of a cancer associated with a KIF5B-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a patient, wherein the patient is selected according to a method, comprising:

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

acquiring genotype information that identifies the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide as being in the patient,

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

23. The use of claim 22, wherein the cancer is chosen from a lung cancer, a pancreatic cancer, a melanoma, a colorectal cancer, an esophageal-gastric cancer, a thyroid cancer, or an adenocarcinoma.

24. The use of claim 22 or 23, wherein the method further comprises providing a report to another party.

25. The use of claim 24, wherein the party is the patient, a caregiver, a physician, an oncologist, a hospital, a clinic, a third-party payor, an insurance company, or a government office.

26. The use of claim 24 or 25, wherein said report is in an electronic, web-based, or paper form.

27. The use of any of claims 24-26, wherein the report identifies the presence or absence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in the patient, and optionally includes an identifier for the patient.

28. The use of any of claims 24-27, wherein said report comprises;
information on the role of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide, or a wildtype sequence, in a 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 the patient; or
information, or a recommendation on, the administration of a drug.

29. A method for generating a personalized cancer treatment report, by detecting a KIF5B-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a tumor sample from a patient, and selecting a RET-kinase inhibitor for the patient based on an identification of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in the tumor sample.

30. The use of any of claims 1-28, or the method of claim 29, wherein the KIF5B-RET fusion polypeptide is an in-frame fusion polypeptide comprising at least the amino acid sequence encoded by exon 15 of KIF5B, and at least the amino acid sequence encoded by exon 12 of RET of SEQ ID NO: 1.

31. The use of any of claims 1-28 or 30, or the method of claim 29 or 30, wherein the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide comprises nucleotides 1720-1731, 1717-1734, or 1714-1737 of SEQ ID NO: 1.

32. The use of any of claims 1-28, 30 or 31, or the method of any of claims 29-31, wherein the KIF5B-RET fusion polypeptide comprises a RET tyrosine kinase domain, and a KIF5B kinesin motor domain and coiled-coil domain, of SEQ ID NO: 2.

33. The use of any of claims 1-28 or 30-32, or the method of any of claim 29-32, wherein the KIF5B-RET fusion polypeptide comprises amino acids 1-575 of SEQ ID NO: 2 corresponding to KIF5B and amino acids 576-977 of SEQ ID NO: 2 corresponding to RET.

We Claims:

1. Use of a RET kinase inhibitor for the manufacture of a medicament for the treatment of a cancer in a subject, wherein the RET kinase inhibitor is to be administered responsive to a determination of a presence of a Kinesin Family Member 5B (KIF5B)-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in said cancer, wherein the cancer is a lung cancer or a colorectal cancer, wherein the RET kinase inhibitor is chosen from cabozantinib, lenvatinib, or vandetanib.

2. The use of claim 1, wherein the RET kinase inhibitor is to be administered responsive to the determination of the presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a tumor sample from said subject.

3. The use of claim 2, wherein the tumor sample:

- (i) comprises fluid, cells, and/or a tissue;
- (ii) is a nucleic acid sample or a protein sample; and/or
- (iii) comprises a tumor biopsy or a circulating tumor cell or nucleic acid.

4. The use of any of claims 1-3, wherein:

(i) the level or activity of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is evaluated;

(ii) the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is detected prior to initiating, during, or after, the treatment of the subject;

(iii) the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is detected at the time of diagnosis of the subject with the cancer; and/or

(iv) the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is detected at a pre-determined interval.

5. The use of any of claims 1-4, wherein the determination of the presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide comprises acquiring knowledge or information of the presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in said subject from another party.

6. The use of any of claims 1-5, wherein a communication of the presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a subject is received.

7. The use of any of claims 1-6, wherein the presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is determined by a method chosen from one or more of: a nucleic acid hybridization assay, an amplification-based assay, a PCT-RFLP assay, real-time PCR, sequencing, a screening analysis, FISH, spectral karyotyping or MFISH, comparative genomic hybridization, *in situ* hybridization, SSP, HPLC, or mass-spectrometric genotyping.

8. The use of any of claims 1-7, wherein said cancer is a lung cancer.

9. The use of claim 8, wherein said lung cancer is chosen from: a small cell lung cancer (SCLC), an adenocarcinoma of the lung, a bronchogenic carcinoma, a non-small cell lung cancer (NSCLC), a squamous cell carcinoma (SCC), or a combination thereof.

10. The use of claim 9, wherein the lung cancer is a non-small cell lung cancer (NSCLC).

11. The use of claim 9, wherein the lung cancer is a squamous cell carcinoma (SCC).

12. The use of any of claims 1-7, wherein the cancer is a colorectal cancer.

13. The use of any of claims 1-12, wherein the RET kinase inhibitor is cabozantinib.

14. The use of any of claims 1-12, wherein the RET kinase inhibitor is lenvatinib.
15. The use of any of claims 1-12, wherein the RET kinase inhibitor is vandetanib.
16. The use of any of claims 1-15, wherein the RET kinase inhibitor is administered in combination with a second therapeutic agent or a different therapeutic modality.
17. Use of a RET kinase inhibitor for the manufacture of a medicament for the treatment of a cancer associated with a KIF5B-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a patient, wherein the patient is selected according to a method, comprising:
 - identifying, selecting, or obtaining information or knowledge that the patient has participated in a clinical trial or has been treated for the cancer;
 - acquiring genotype information that identifies the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide as being in the patient,
 - identifying the patient as having an increased risk for, or having, the cancer associated with the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide by detecting a presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide,
 - wherein the cancer is a lung cancer or a colorectal cancer, and wherein the RET kinase inhibitor is chosen from cabozantinib, lenvatinib, or vandetanib.
18. The use of claim 17, wherein the method further comprises providing a report to a party.
19. The use of claim 18, wherein the party is the patient, a caregiver, a physician, an oncologist, a hospital, a clinic, a third-party payor, an insurance company, or a government office.

20. The use of claim 18 or 19, wherein said report is in an electronic, web-based, or paper form.

21. The use of any of claims 18-20, wherein the report identifies the presence or absence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in the patient, and optionally includes an identifier for the patient.

22. The use of any of claims 18-21, wherein said report comprises;
information on the role of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide, or a wildtype sequence, in a 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 the patient; or
information, or a recommendation on, the administration of a drug.

23. A method for generating a personalized cancer treatment report, by detecting a KIF5B-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a tumor sample from a patient, and selecting a RET kinase inhibitor for the patient based on an identification of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in the tumor sample, wherein the cancer is a lung cancer or a colorectal cancer, and wherein the RET kinase inhibitor is chosen from cabozantinib, lenvatinib, or vandetanib.

24. The use of any of claims 1-22, or the method of claim 23, wherein the KIF5B-RET fusion polypeptide is an in-frame fusion polypeptide comprising at least the amino acid sequence encoded by exon 15 of KIF5B, and at least the amino acid sequence encoded by exon 12 of RET of SEQ ID NO: 1.

25. The use of any of claims 1-22 or 24, or the method of claim 23 or 24, wherein the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide comprises nucleotides 1720-1731, 1717-1734, or 1714-1737 of SEQ ID NO: 1.

26. The use of any of claims 1-22, 24, or 25, or the method of any of claims 23-25, wherein the KIF5B-RET fusion polypeptide comprises a RET tyrosine kinase domain, and a KIF5B kinesin motor domain and coiled-coil domain, of SEQ ID NO: 2.

27. The use of any of claims 1-22 or 24-26, or the method of any of claims 23-26, wherein the KIF5B-RET fusion polypeptide comprises amino acids 1-575 of SEQ ID NO: 2 corresponding to KIF5B and amino acids 576-977 of SEQ ID NO: 2 corresponding to RET.