

METHODS OF TREATING CANCER

BACKGROUND

[0001] Soluble forms of Fibroblast Growth Factor Receptor 1 (FGFR1) have been shown to inhibit tumor cell growth *in vitro* and *in vivo*. See, e.g., U.S. Patent No. 7,678,890. The efficacy of anti-cancer therapies is, in some instances, dependent on the genetic makeup of the cancer being targeted.

SUMMARY

[0002] In one example, there is described the use of a fibroblast growth factor receptor 1 (FGFR1) extracellular domain (ECD) or an FGFR1 ECD fusion molecule for preparation of a medicament for treating cancer in a subject, wherein the cancer is characterized by a higher level of FGF2 compared to the level of VEGF, wherein said higher level of FGF2 compared to the level of VEGF indicates therapeutic responsiveness by the cancer to a fibroblast growth factor receptor 1 (FGFR1) extracellular domain (ECD) or an FGFR1 ECD fusion molecule. In another example, there is disclosed the use of an FGFR1 ECD or an FGFR1 ECD fusion molecule for preparation of a medicament for treating cancer in a subject, wherein the cancer is characterized by a lower level of FGF2 compared to the level of VEGF, wherein the medicament comprises an FGFR1 ECD or an FGFR1 ECD fusion molecule, FGFR1 ECD or an FGFR1 ECD fusion molecule and a therapeutically effective amount of at least one anti-angiogenic agent, and wherein said lower level of FGF2 compared to the level of VEGF indicates therapeutic responsiveness by the cancer to an FGFR1 ECD or an FGFR1 ECD fusion molecule, FGFR1 ECD or an FGFR1 ECD fusion molecule and a therapeutically effective amount of at least one anti-angiogenic agent. In a further example, there is disclosed the use of an FGFR1 ECD or FGFR1 ECD fusion molecule for preparation of a medicament for reducing blood vessel density in a solid cancer. In yet another example, there is disclosed the use of an FGFR1 ECD or FGFR1 ECD fusion molecule for preparation of a medicament for treating mesothelioma in a subject, wherein the medicament comprises the FGFR1 ECD or FGFR1 ECD fusion molecule and at least one therapeutic agent selected from paclitaxel, carboplatin, docetaxel, pemetrexed, and cisplatin. In one example, there is described a method of identifying a subject who may benefit from treatment with an FGFR1 ECD or an FGFR1 ECD fusion molecule, the method comprising determining the levels of FGF2 and VEGF in a sample obtained from the subject, wherein a higher level of FGF2 compared to the level of VEGF in the sample indicates that the subject may benefit from treatment with the fibroblast growth factor receptor 1 (FGFR1) extracellular domain (ECD) or an FGFR1 ECD fusion molecule. In another example, there is disclosed a method of

cancer are provided, wherein the cancer has a higher level of FGF2 compared to the level of VEGF. In some examples, methods of reducing blood vessel density in a VEGF-resistant solid cancer are provided. In some examples, a method of reducing blood vessel density in a solid cancer comprises administering to a subject with cancer an FGFR1 ECD or FGFR1 ECD fusion molecule. In some examples, blood vessel density is measured in the whole tumor sample. In some examples, the cancer is selected from kidney cancer (such as renal cell carcinoma), liver cancer (such as hepatocellular carcinoma), lung cancer, colon cancer, liver cancer, breast cancer, stomach cancer, ovarian cancer, endometrial cancer, esophageal cancer, head and neck cancer, glioblastoma, mesothelioma, and prostate cancer. In some examples, the cancer is selected from kidney cancer (such as renal cell carcinoma), liver cancer (such as hepatocellular carcinoma), glioblastoma, and mesothelioma. In some examples, the cancer is renal cell carcinoma. In some examples, the cancer is hepatocellular carcinoma. In some examples, the cancer is mesothelioma.

[0024] In some examples, methods of treating mesothelioma are provided, comprising administering to a subject with mesothelioma an FGFR1 ECD or FGFR1 ECD fusion molecule and at least one therapeutic agent selected from paclitaxel, carboplatin, docetaxel, pemetrexed, and cisplatin. In some examples, the method comprises administering an FGFR1 ECD or FGFR1 ECD fusion molecule, paclitaxel and carboplatin. In some examples, the method comprises administering an FGFR1 ECD or FGFR1 ECD fusion molecule and docetaxel. In some examples, the method comprises administering an FGFR1 ECD or FGFR1 ECD fusion molecule, pemetrexed, and cisplatin. In some examples, administration of the FGFR1 ECD or FGFR1 ECD fusion molecule and at least one therapeutic agent reduces blood vessel density in the mesothelioma. In some examples, the mesothelioma has a high level of FGF2. In some examples, the mesothelioma has a higher level of FGF2 compared to the level of VEGF. In some examples, the ratio of FGF2 level to VEGF level is greater than 1.

[0025] In any of the methods described herein, the method may comprise administering an FGFR1 ECD. In some examples, the FGFR1 ECD comprises an amino acid sequence selected from SEQ ID NOs: 1 to 4.

[0026] In any of the methods described herein, the method may comprise administering an FGFR1 ECD fusion molecule. In some examples, the FGFR1 ECD fusion molecule comprises an FGFR1 ECD and a fusion partner, and wherein the fusion partner is Fc. In some examples, the FGFR1 ECD fusion molecule comprises a sequence selected from SEQ ID NO: 5 and SEQ ID NO: 6. In one aspect, the present invention refers to use of a fibroblast growth factor receptor 1 (FGFR1) extracellular domain (ECD) fusion molecule for preparation of a medicament for treating cancer in a subject, wherein the cancer is characterized by a higher level of FGF2 compared to the level of VEGF, wherein said higher level of FGF2 compared to the level of VEGF indicates therapeutic responsiveness by the cancer to an FGFR1 ECD fusion molecule, wherein the FGFR1 ECD fusion molecule comprises a sequence selected from SEQ ID NO: 5 and SEQ ID NO: 6.

reducing blood vessel density in a solid cancer. In one example, said solid cancer has a higher level of FGF2 compared to the level of VEGF.

[0037] In a further example of the disclosure is provided an FGFR1 ECD or FGFR1 ECD fusion molecule and at least one therapeutic agent selected from paclitaxel, carboplatin, docetaxel, pemetrexed and cisplatin for use in the treatment of mesothelioma. In one example, said treatment involves the use of an FGFR1 ECD or FGFR1 ECD fusion molecule, paclitaxel and carboplatin. In one example said treatment involves the use of an FGFR1 ECD or FGFR1 ECD fusion molecule and docetaxel. In one example, said treatment involves the use of an FGFR1 ECD or FGFR1 ECD fusion molecule, pemetrexed, and cisplatin. In any of these examples, administration of the FGFR1 or FGFR1 ECD fusion molecule and at least one therapeutic agent reduces the blood vessel density in said mesothelioma.

[0038] In a further example of the disclosure is provided the use of FGFR1 ECD or FGFR1 ECD fusion molecule and at least one therapeutic agent selected from paclitaxel, carboplatin, docetaxel, pemetrexed and cisplatin in the manufacture of a medicament for use in the treatment of mesothelioma. In one example, said medicament comprises an FGFR1 ECD or FGFR1 ECD fusion molecule, paclitaxel and carboplatin. In one example said medicament comprises an FGFR1 ECD or FGFR1 ECD fusion molecule and docetaxel. In one example, said medicament comprises an FGFR1 ECD or FGFR1 ECD fusion molecule, pemetrexed, and cisplatin. In any of these examples, administration of said medicament reduces the blood vessel density in said mesothelioma.

[0039] In any examples, the FGF2 level or VEGF level may be mRNA levels. In one example, the mRNA level may be determined by quantitative RT-PCR.

[0040] Further, in any examples, the FGF2 level or VEGF level may be protein levels. In one example, the protein level may be determined by immunohistochemistry.

[0041] In any examples, the anti-angiogenic agent is a VEGF antagonist. In a further example, the VEGF antagonist is selected from pazopanib, bevacizumab, axitinib, aflibercept, sorafenib, or sunitinib.

[0042] In any examples, the cancer is selected from kidney cancer (such as renal cell carcinoma), liver cancer (such as hepatocellular carcinoma), lung cancer, colon cancer, liver cancer, breast cancer, stomach cancer, ovarian cancer, endometrial cancer, esophageal cancer, head and neck cancer, glioblastoma, and prostate cancer. In one aspect, the present invention refers to a method of identifying a subject who may benefit from treatment with an FGFR1 ECD fusion molecule, the method comprising determining the levels of FGF2 and VEGF in a sample obtained from the subject, wherein a higher level of FGF2 compared to the level of VEGF in the sample indicates that the subject may benefit from treatment with the FGFR1 ECD fusion molecule.

CLAIMS

1. Use of a fibroblast growth factor receptor 1 (FGFR1) extracellular domain (ECD) fusion molecule for preparation of a medicament for treating cancer in a subject, wherein the cancer is characterized by a higher level of FGF2 compared to the level of VEGF, wherein said higher level of FGF2 compared to the level of VEGF indicates therapeutic responsiveness by the cancer to an FGFR1 ECD fusion molecule, wherein the FGFR1 ECD fusion molecule comprises a sequence selected from SEQ ID NO: 5 and SEQ ID NO: 6.
2. The use of claim 1, wherein least a portion of the cells of the subject's cancer have been determined to have a higher level of FGF2 compared to the level of VEGF prior to treatment with the FGFR1 ECD or FGFR1 ECD fusion molecule.
3. The use of claim 1 or 2, wherein the FGF2 level is FGF2 mRNA level and the VEGF level is VEGF mRNA level.
4. The use of claim 1 or 2, wherein the FGF2 level is FGF2 protein level and the VEGF level is VEGF protein level.
5. The use of any one of claims 1 to 4, wherein the ratio of FGF2 level to VEGF level is greater than 1.
6. The use of any one of claims 1 to 5, wherein the cancer is responsive to a FGFR1 ECD or a FGFR1 ECD fusion molecule as a monotherapy.
7. The use of any one of claims 1 to 6, wherein the treatment comprises administration of a FGFR1 ECD or a FGFR1 ECD fusion molecule as a monotherapy.
8. The use of any one of claims 1 to 7, wherein the cancer is selected from kidney cancer (such as renal cell carcinoma), liver cancer (such as hepatocellular carcinoma), lung cancer, colon cancer, liver cancer, breast cancer, stomach cancer, ovarian cancer, endometrial cancer, esophageal cancer, head and neck cancer, glioblastoma, mesothelioma, and prostate cancer.

9. The use of claim 8, wherein the cancer is mesothelioma.
10. The use of any one of claims 1 to 8, wherein the subject has previously been treated with at least one therapeutic agent selected from pazopanib, bevacizumab, axitinib, aflibercept, sorafenib, and sunitinib.
11. The use of claim 10, wherein the subject has a VEGF-resistant cancer or a pazopanib-resistant cancer.
12. A method of identifying a subject who may benefit from treatment with an FGFR1 ECD fusion molecule, the method comprising determining the levels of FGF2 and VEGF in a sample obtained from the subject, wherein a higher level of FGF2 compared to the level of VEGF in the sample indicates that the subject may benefit from treatment with the FGFR1 ECD fusion molecule.