Publication No. WO 1998/045331; Baca, M. *et al*. (1997) "*Antibody Humanization Using Monovalent Phage Display*," J. Biol. Chem. 272(16):10678-10684; Presta, L.G. *et al*. (1997) "*Humanization Of An Anti-Vascular Endothelial Growth Factor Monoclonal Antibody For The Therapy Of Solid Tumors And Other Disorders*," Cancer Res. 57(20):4593-4599; each of which documents is herein incorporated by reference in its entirety.

[0026] Unfortunately, recurrent glioblastomas (rGBM) invariably relapse after initial response to anti-VEGF therapy (di Tomaso, E. *et al*. (2011) "*Glioblastoma Recurrence after Cediranib Therapy in Patients: Lack of "Rebound" Revascularization as Mode of Escape*," Cancer Res. 71:19-28.

[0027] Thus, despite all prior advances, a need remains for improved compositions for treating vascularizing cancers, and glioblastoma, in particular. The present invention is directed to such compositions and to their use in the treatment of glioblastoma and other cancers involving vascularization.

Summary:

[0028] The disclosure concerns therapeutic compositions for the treatment of vascularizing cancers, especially, glioblastoma. In particular, the disclosure is directed to compositions that comprise a molecule having a binding ability that is specific for B7-H3 and a molecule having a binding ability that is specific for a cell-surface factor (or its receptor) that is involved in promoting tumor angiogenesis (especially VEGF or its receptor, VEGFR). The disclosure is additionally directed to the use of such compositions in the treatment of such cancers, and in particular, in the treatment of glioblastoma.

[0028a] In one aspect, there is provided use of an antibody, an antibody fragment thereof, or a diabody that is specific for B7-H3, and an antibody, or an antibody fragment thereof, that is specific for VEGF or VEGFR, in the manufacture of a medicament for combination therapy for the treatment of glioblastoma.

[0028b] Also provided is use of a molecule having a binding ability that is specific for B7-H3 in the manufacture of a medicament for treating a vascularizing cancer in a recipient patient in need thereof, wherein the molecule having a binding ability that is specific for B7-H3 is to be administered with a molecule having a binding ability that is specific for a cell-surface factor, or a receptor therefor, that promotes tumor angiogenesis.

[0028c] In another aspect, there is provided use of an antibody, an antibody fragment thereof, or a diabody that is specific for B7-H3, in the manufacture of a medicament for the treatment of glioblastoma, wherein said antibody, antibody fragment, or diabody that is specific for B7-H3 is to be administered concurrently or sequentially in combination with an antibody, or an antibody fragment thereof, that is specific for VEGF or VEGFR.

[0029] In detail, the disclosure provides a method of treating a vascularizing cancer comprising administering to a recipient patient in need thereof, a molecule having a binding ability that is specific for B7-H3 and a molecule having a binding ability that is specific for a cell-surface factor, or a receptor therefor, that promotes tumor angiogenesis.

[0030] The disclosure particularly concerns the example of such method wherein the molecule having the binding ability that is specific for B7-H3 is:

(A) an anti-B7-H3 antibody;

(B) a B7-H3-binding fragment of (A); or

(C) a diabody that binds B7-H3.

[0031] The disclosure particularly concerns the example of such methods wherein the molecule having the binding ability that is specific for a cell-surface factor, or a receptor therefor, that promotes tumor angiogenesis is:

(A) an anti-VEGF antibody or a VEGF antagonist; or

(B) an anti-VEGFR antibody or a VEGFR antagonist.

[0032] The disclosure particularly concerns the example of such methods wherein the molecule having the binding ability that is specific for B7-H3:

A. competes for B7-H3 binding with antibodies BRCA84D, BRCA69D, or PRCA157; or

B. has the three heavy chain CDRs and the three light chain CDRs of antibody BRCA84D, of antibody BRCA69D, or of antibody PRCA157.

[0033] The disclosure additionally concerns the example of such methods wherein the molecule having the binding ability that is specific for a cell-surface factor, or a receptor therefor, that promotes tumor angiogenesis:

A. competes for VEGF binding with bevacizumab; or

B. has the three heavy chain CDRs and the three light chain CDRs of bevacizumab.

[0034] The disclosure additionally concerns the example of such methods wherein the molecule having the binding ability that is specific for B7-H3 is an anti-B7-H3 antibody having:

(A) a light chain variable domain that comprises the CDR1, CDR2 and CDR3 of the light chain of BRCA84D;

(B) a heavy chain variable domain that comprises the CDR1 CDR2 and CDR3 of the heavy chain of BRCA84D; and

(C) an Fc region that comprises the substitutions: L235V, F243L, R292P, Y300L, and P396L.

[0035] The disclosure concerns the example of such methods wherein the molecule having the binding ability that is specific for B7-H3 is a humanized anti-B7-H3 antibody that comprises:

(A) a variable light chain having the amino acid sequence of hBRCA84D-2 VL (**SEQ ID NO:69**); and

(B) a variable heavy chain having the amino acid sequence of hBRCA84D-2 VH (**SEQ ID NO:79**);

and the molecule having the binding ability that is specific for a cell-surface factor, or a receptor therefor, that promotes tumor angiogenesis is bevacizumab.

[0036] The disclosure additionally concerns the example of such methods wherein the molecule having the B7-H3 binding ability and the molecule having the VEGF-binding ability are administered to the patient, and the two molecules are administered concurrently.

[0037] The disclosure additionally concerns the example of such methods wherein the second of the administered molecules is administered to the patient within 5 half-lives after the administration of the first of the molecule.

[0038] The disclosure additionally concerns the example of such methods wherein the vascularizing cancer is glioblastoma.

[0039] The disclosure additionally concerns the example of such methods wherein the molecule has the binding ability that is specific for B7-H3 and the molecule having the binding ability that is specific for a cell-surface factor, or a receptor therefor, that promotes tumor angiogenesis are the same molecule, the molecule being a bi-specific antibody or a bi-specific diabody.

Brief Description of the Drawings:

[0040] **Figure 1** shows MRI scans of glioblastoma Patient NF. The first, second and third columns are, respectively, MRI scans of a first, second and third observed lesion.

What Is Claimed Is:

Claim 1. Use of an antibody, an antibody fragment thereof, or a diabody that is specific for B7-H3, and an antibody, or an antibody fragment thereof, that is specific for VEGF or VEGFR, in the manufacture of a medicament for combination therapy for the treatment of glioblastoma.

Claim 2. Use of an antibody, an antibody fragment thereof, or a diabody that is specific for B7-H3, in the manufacture of a medicament for the treatment of glioblastoma, wherein said antibody, antibody fragment, or diabody that is specific for B7-H3 is to be administered concurrently or sequentially in combination with an antibody, or an antibody fragment thereof, that is specific for VEGF or VEGFR.

Claim 3. The use of any one of claims 1-2, wherein said antibody, or antibody fragment thereof, that is specific for VEGF or VEGFR is:

(A) a VEGF antagonist; or

(B) a VEGFR antagonist.

Claim 4. The use of any one of claims 1-3, wherein said antibody, antibody fragment thereof, or diabody that is specific for B7-H3 comprises:

(1) a light chain variable domain that comprises CDR_1 having the amino acid sequence of SEQ ID NO: 7, CDR_2 having the amino acid sequence of SEQ ID NO: 9 and CDR_3 having the amino acid sequence of SEQ ID NO: 11, and a heavy chain variable domain that comprises CDR_1 having the amino acid sequence of SEQ ID NO: 15, CDR_2 having the amino acid sequence of SEQ ID NO: 17 and CDR_3 having the amino acid sequence of SEQ ID NO: 19; or

(2) a light chain variable domain that comprises CDR_1 having the amino acid sequence of SEQ ID NO: 23, CDR_2 having the amino acid sequence of SEQ ID NO: 25 and CDR_3 having the amino acid sequence of SEQ ID NO: 27, and a heavy chain variable domain that comprises CDR_1 having the amino acid sequence of

SEQ ID NO: 31, CDR_2 having the amino acid sequence of SEQ ID NO: 33 and CDR_3 having the amino acid sequence of SEQ ID NO: 35; or

(3) a light chain variable domain that comprises CDR_1 having the amino acid sequence of SEQ ID NO: 39, CDR_2 having the amino acid sequence of SEQ ID NO: 41 and CDR_3 having the amino acid sequence of SEQ ID NO: 43, and a heavy chain variable domain that comprises CDR_1 having the amino acid sequence of SEQ ID NO: 47, CDR_2 having the amino acid sequence of SEQ ID NO: 49 and CDR_3 having the amino acid sequence of SEQ ID NO: 51.

Claim 5. The use of any one of claims 1-4, wherein said antibody, or antibody fragment thereof, that is specific for VEGF or VEGFR comprises the three heavy chain CDRs and the three light chain CDRs of bevacizumab.

Claim 6. The use of any one of claims 1-5, wherein said antibody, antibody fragment thereof, or diabody that is specific for B7-H3 is an anti-B7-H3 antibody comprising:

(A) a light chain variable domain that comprises CDR_1 having the amino acid sequence of SEQ ID NO: 39, CDR_2 having the amino acid sequence of SEQ ID NO: 41 and CDR_3 having the amino acid sequence of SEQ ID NO: 43;

(B) a heavy chain variable domain that comprises CDR_1 having the amino acid sequence of SEQ ID NO: 47, CDR_2 having the amino acid sequence of SEQ ID NO: 49 and CDR_3 having the amino acid sequence of SEQ ID NO: 51; and

(C) an Fc region that comprises the substitutions: L235V, F243L, R292P, Y300L, and P396L.

Claim 7. The use of claim 6, wherein said antibody, antibody fragment thereof, or diabody that is specific for B7-H3 is a humanized anti-B7-H3 antibody that comprises:

(A) a variable light chain having the amino acid sequence of **SEQ ID NO:69**; and

(B) a variable heavy chain having the amino acid sequence of **SEQ ID NO:79**;

and said antibody, or antibody fragment thereof, that is specific for VEGF or VEGFR is bevacizumab.

Claim 8. The use of any one of claims 2-7, wherein said antibody, antibody fragment thereof, or diabody that is specific for B7-H3 and said antibody, or antibody fragment thereof, that is specific for VEGF or VEGFR are to be administered concurrently.

Claim 9. The use of any one of claims 2-7, wherein said antibody, antibody fragment thereof, or diabody that is specific for B7-H3, and said antibody, or antibody fragment thereof, that is specific for VEGF or VEGFR are to be administered sequentially.