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 a composition comprising:

a) an antibody, an antibody fragment thereof, or a diabody that is specific for B7-H3; and

b) an antibody, or an antibody fragment thereof, that is specific for VEGF or VEGFR;

for use in treating 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 combination with an antibody, or an antibody fragment thereof, that is specific for VEGF or VEGFR, in the manufacture of a medicament for treating glioblastoma.

[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.

What Is Claimed Is:

Claim 1. A composition comprising:

a) an antibody, an antibody fragment thereof, or a diabody that is specific for B7-H3; and

b) an antibody, or an antibody fragment thereof, that is specific for VEGF or VEGFR;

for use in treating glioblastoma.

Claim 2. Use of an antibody, an antibody fragment thereof, or a diabody that is specific for B7-H3 in combination with an antibody, or an antibody fragment thereof, that is specific for VEGF or VEGFR, in the manufacture of a medicament for treating glioblastoma.

Claim 3. The composition of claim 1, or the use of claim 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 composition of any one of claims 1 or 3, or the use of any one of claims 2 or 3, wherein said antibody, antibody fragment thereof, or diabody that is specific for B7-H3 competes for binding to said B7-H3 with an antibody that 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;

(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 composition of any one of claims 1 or 3-4, or the use of any one of claims 2-4, 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;

(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 6. The composition of any one of claims 1 or 3-5, or the use of any one of claims 2-5, wherein said antibody, or antibody fragment thereof, that is specific for VEGF or VEGFR:

A. competes for VEGF binding with bevacizumab; or

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

Claim 7. The composition of any one of claims 1 or 3-6, or the use of any one of claims 2-4 or 6, wherein said antibody, antibody fragment thereof, or diabody that is specific for B7-H3 is an anti-B7-H3 antibody having:

(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 8. The composition of claim 7, or the use of claim 7, 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 9. The use of any one of claims 2-8, 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 10. The use of any one of claims 2-8, wherein the second of said antibody, antibody fragment thereof, or diabody that is specific for B7-H3, or said antibody, or antibody fragment thereof, that is specific for VEGF or VEGFR is to be administered to said patient within 5 half-lives after the administration of the first of said antibody, antibody fragment thereof, or diabody that is specific for B7-H3, or said antibody, or antibody fragment thereof, that is specific for VEGF or VEGFR.