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 ~~of the Invention~~:

[0028] The ~~invention~~ disclosure concerns therapeutic compositions for the treatment of vascularizing cancers, especially, glioblastoma. In particular, the ~~invention~~ 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~~invention~~ 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 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.

[0029] In detail, the disclosure~~invention~~ 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~~invention~~ particularly concerns the embodiment 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~~invention~~ particularly concerns the embodiment 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~~invention~~ particularly concerns the embodiment 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~~invention~~ additionally concerns the embodiment 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~~invention~~ additionally concerns the embodiment 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~~invention~~ concerns the embodiment 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~~invention~~ additionally concerns the embodiment 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~~invention~~ additionally concerns the embodiment 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~~invention~~ additionally concerns the embodiment of such methods wherein the vascularizing cancer is glioblastoma.

[0039] The disclosure~~invention~~ additionally concerns the embodiment 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. 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.

Claim 2. The method of claim 1, wherein said molecule having said 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.

Claim 3. The method of any one of claims 1-2, wherein said molecule having said 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.

Claim 4. The method of any of claims 1-3, wherein said molecule having said 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.

Claim 5. The method of any of claims 1-4, wherein said molecule having said 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.

Claim 6. The method of claim 1, wherein said molecule having said binding ability that is specific for B7-H3 is an anti-B7-H3 antibody having:

(A) a light chain variable domain that comprises the CDR_1, CDR_2 and CDR_3 of the light chain of BRCA84D;

(B) a heavy chain variable domain that comprises the CDR_1, CDR_2 and CDR_3 of the heavy chain of BRCA84D; and

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

Claim 7. The method of claim 6, wherein said molecule having said 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 said molecule having said binding ability that is specific for a cell-surface factor, or a receptor therefor, that promotes tumor angiogenesis is bevacizumab.

Claim 8. The method of any of claims 3-7, wherein said molecule having said B7-H3 binding ability and said molecule having said VEGF-binding ability are administered to said patient, and said two molecules are administered concurrently.

Claim 9. The method of claim 8, wherein the second of said administered molecules is administered to said patient within 5 half-lives after the administration of the first of said molecule.

Claim 10. The method of any of claims 1-9, wherein said vascularizing cancer is glioblastoma.

Claim 11. The method of claim 1, wherein said molecule having said binding ability that is specific for B7-H3 and said molecule having said binding ability

that is specific for a cell-surface factor, or a receptor therefor, that promotes tumor angiogenesis are the same molecule, said molecule being a bi-specific antibody or a bi-specific diabody.

What Is Claimed Is:

Claim 1. 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.

Claim 2. The use of claim 1, wherein said molecule having said 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.

Claim 3. The use of any one of claims 1-2, wherein said molecule having said 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.

Claim 4. The use of any of claims 1-3, wherein said molecule having said 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.

Claim 5. The use of any of claims 1-4, wherein said molecule having said 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.

Claim 6. The use of claim 1, wherein said molecule having said binding ability that is specific for B7-H3 is an anti-B7-H3 antibody having:

(A) a light chain variable domain that comprises the CDR_1, CDR_2 and CDR_3 of the light chain of BRCA84D;

(B) a heavy chain variable domain that comprises the CDR_1 CDR_2 and CDR_3 of the heavy chain of BRCA84D; and

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

Claim 7. The use of claim 6, wherein said molecule having said 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 said molecule having said binding ability that is specific for a cell-surface factor, or a receptor therefor, that promotes tumor angiogenesis is bevacizumab.

Claim 8. The use of any of claims 3-7, wherein said molecule having said B7-H3 binding ability and said molecule having said VEGF-binding ability are to be administered to said patient, and said two molecules are to be administered concurrently.

Claim 9. The use of claim 8, wherein the second of said administered molecules is to be administered to said patient within 5 half-lives after the administration of the first of said molecule.

Claim 10. The use of any of claims 1-9, wherein said vascularizing cancer is glioblastoma.

Claim 11. The use of claim 1, wherein said molecule having said binding ability that is specific for B7-H3 and said molecule having said binding ability that is specific for a cell-surface factor, or a receptor therefor, that promotes tumor angiogenesis are the same molecule, said molecule being a bi-specific antibody or a bi-specific diabody.