VISTA ANTIGEN-BINDING MOLECULES

FIELD OF THE INVENTION

[0001] The present invention relates to the fields of molecular biology, more specifically antibody technology. The present invention also relates to methods of medical treatment and prophylaxis.

BACKGROUND TO THE INVENTION

[0002] Myeloid Derived Suppressor Cell (MDSC)-mediated suppression of immune response has been identified in multiple solid tumors and lymphomas. MDSCs are elevated in advanced colorectal cancer (Toor et al, Front Immunol. 2016; 7:560). MDSCs are also observed in breast cancer, and the percentage of MDSCs in the peripheral blood is increased in patients with later stage breast cancer (Markowitz et al, Breast Cancer Res Treat. 2013 July; 140(1):13-21). MDSC abundance is also correlated with poor prognosis in solid tumors (Charoentong et al, Cell Rep. 2017 Jan. 3; 18(1):248-262).

[0003] MDSCs exert suppression over T cells through multiple mechanisms, including the production of reactive oxygen species, nitric oxide, and arginase. These ultimately lead to suppression of DC, NK and T cell activity and increased tumor burden (Umansky et al., Vaccines (Basel) (2016) 4(4):36). MDSCs also contribute to the tumor development and metastasis through the production of soluble factors such as matrix metalloproteinases, VEGF, bFGF, TGF-β and S100A8/A9 which promote neovascularisation, invasion, proliferation and metastasis.

[0004] Targeting V-type immunoglobulin domain-containing suppressor of T-cell activation (VISTA), an immune checkpoint inhibitor expressed primarily on MDSCs, is an attractive therapeutic strategy for removing MDSC-mediated suppression of effector immune cell function.

[0005] WO 2017/137830 A1 discloses anti-VISTA antibody VSTB174, which is disclosed at e.g. paragraph [00221] to comprise the variable regions of anti-VISTA antibody VSTB112. Paragraph [00362] discloses that VSTB123 comprises the variable regions of VSTB174. Example 25 of WO 2017/137830 A1 at paragraph [0417] and FIG. **42**A disclose that mIgG2a antibody VSTB123 was able to inhibit tumor growth in a MB49 tumor model. Paragraph [0418] and FIG. **42**A disclose that by contrast VSTB124—which is the same antibody provided in IgG2a LALA format; see paragraph [0408]—did not inhibit tumor growth. Based on these results Example 25 concludes at paragraph [0419] that efficacy with anti-VISTA antibody treatment might require active Fc. Accordingly, the proposed mechanism of action for the anti-VISTA antibody represented schematically at FIG. **47** (see the legend to FIG. **47** at paragraph [0053]) involves Fc-mediated engagement of FcγRIII expressed by NK cells.

[0006] Hamster monoclonal anti-VISTA antibody mAb13F3 is disclosed in Le Mercier et al. Cancer Res. (2014) 74(7):1933-44 to inhibit tumor growth in B16OVA and B16-BL6 melanoma models. Page 1942, paragraph spanning left and right columns teaches that immunogenicity and the FcR binding activity of the VISTA mAb might be critical limiting factors for achieving optimal target neutralization and therapeutic efficacy.

SUMMARY OF THE INVENTION

[0007] In a first aspect the present invention provides an antigen-binding molecule, optionally isolated, which is capable of binding to VISTA and inhibiting VISTA-mediated signalling, independently of Fc-mediated function.

[0008] Also provided is an antigen-binding molecule, optionally isolated, which is capable of binding to VISTA and inhibiting VISTA-mediated signalling, wherein the antigen-binding molecule is not able to induce an Fc-mediated antibody effector function.

[0009] In some embodiments the antigen-binding molecule is not able to induce antibody-dependent cellular cytotoxicity (ADCC) and/or is not able to induce antibody-dependent cell-mediated phagocytosis (ADCP) and/or is not able to induce complement-dependent cytotoxicity (CDC).

[0010] Also provided is an antigen-binding molecule, optionally isolated, which is capable of binding to VISTA and inhibiting VISTA-mediated signalling, wherein the antigen-binding molecule does not bind to an Fcγ receptor and/or wherein the antigen-binding molecule does not bind to C1q.

[0011] In some embodiments the antigen-binding molecule is capable of binding to VISTA in the Ig-like V-type domain.

[0012] In some embodiments the antigen-binding molecule is capable of binding to a polypeptide comprising or consisting of the amino acid sequence of SEQ ID NO:6.

[0013] In some embodiments the antigen-binding molecule is capable of binding to a polypeptide comprising or consisting of the amino acid sequence of SEQ ID NO:31.

[0014] In some embodiments the antigen-binding molecule does not compete with IGN175A for binding to VISTA (e.g. as determined by epitope binning analysis, e.g. as described in Example 8).

[0015] In some embodiments the antigen-binding molecule is not capable of binding to a peptide consisting of the amino acid sequence of SEQ ID NO:275.

[0016] In some embodiments the antigen-binding molecule comprises:

- **[0017]** (i) a heavy chain variable (VH) region incorporating the following CDRs:
  - **[0018]** HC-CDR1 having the amino acid sequence of SEQ ID NO:244
  - **[0019]** HC-CDR2 having the amino acid sequence of SEQ ID NO:34
  - **[0020]** HC-CDR3 having the amino acid sequence of SEQ ID NO:246; and
- **[0021]** (ii) a light chain variable (VL) region incorporating the following CDRs:
  - **[0022]** LC-CDR1 having the amino acid sequence of SEQ ID NO:41
  - **[0023]** LC-CDR2 having the amino acid sequence of SEQ ID NO:245
  - **[0024]** LC-CDR3 having the amino acid sequence of SEQ ID NO:43.

[0025] In some embodiments the antigen-binding molecule comprises:

- **[0026]** (i) a heavy chain variable (VH) region incorporating the following CDRs:
  - **[0027]** HC-CDR1 having the amino acid sequence of SEQ ID NO:33
  - **[0028]** HC-CDR2 having the amino acid sequence of SEQ ID NO:34