

ANTI-TREM1 ANTIBODIES AND RELATED METHODS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/802,161, filed February 6, 2019, and U.S. Provisional Application No. 62/889,994, filed on August 21, 2019, which are hereby incorporated by reference in their entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted via EFS-Web and is hereby incorporated by reference in its entirety. ~~Said ASCII copy, created on February 17, 2020, is named PH-010WO-SL.txt, and is 92,256 bytes in size.~~

BACKGROUND

[0003] Immunity plays a role in preventing tumor outgrowth. A complex microenvironment can develop within the lesion, and despite the recruitment of T-cells, there is often no effective control of the developing mass. Understanding the balance between tumor elimination and tumor escape may rely on a comprehension of the differential roles myeloid cells play in the tumor microenvironment.

[0004] Myeloid populations of the tumor microenvironment prominently include monocytes and neutrophils (sometimes loosely grouped as myeloid-derived suppressor cells), macrophages, and dendritic cells. Although intra-tumoral myeloid populations, as a whole, have long been considered non-stimulatory or suppressive, it has more recently been appreciated that not all tumor-infiltrating myeloid cells are functionally equivalent.

[0005] In normal tissues, many of these myeloid cells are essential for proper functioning of both innate and adaptive immunity and notably for wound repair. However, in the setting of cancer, a significant excess of macrophages and dysfunctional or skewed populations of these and other cell types are commonly described. When considered as an aggregate population defined by single markers, such as CD68 or CD163, "macrophage" infiltration is correlated with worse outcomes in patients across multiple tumor types ((de Visser, Cancer Immunol Immunother, 2008;57:1531–9); (Hanada et al., Int J Urol 2000;7:263–9); (Yao et al. Clin Cancer Res, 520, 2001;7:4021–6); (Ruffell et al., PNAS, 523 2012;109:2796–801)). But the phenotypic and functional subsetting of macrophages from the tumor microenvironment is complicated by the similarity of macrophages and dendritic cells, and is problematic in tumor biology. A morphologic criterion has been often applied to the issue; one approach to try to differentiate dendritic cells from macrophages was based on a more spikey or dendritic morphology for the former and more veiled or bulbous morphology for the latter (Bell et al., J Exp Med 555, 1999;190:1417–26). Other groups are trying to differentiate on the basis of genetic and cell-surface markers.

[0006] There is diversity in the antigen-presenting compartment within tumors, and T-cells can differentiate features of antigen-presenting cells (APC). Because T cells are a major driver of tumor

CLAIMS

1. An isolated antibody that binds to human TREM1 (SEQ ID NO: 1), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:
 - a. CDR-H1 comprises the sequence set forth in SEQ ID NO: 23,
 - b. CDR-H2 comprises the sequence set forth in SEQ ID NO: 24,
 - c. CDR-H3 comprises the sequence set forth in SEQ ID NO: 33,
 - d. CDR-L1 comprises the sequence set forth in SEQ ID NO: 26,
 - e. CDR-L2 comprises the sequence set forth in SEQ ID NO: 27, and
 - f. CDR-L3 comprises the sequence set forth in SEQ ID NO: 28.
2. The isolated antibody of claim 1, wherein the VH sequence comprises the sequence set forth in SEQ ID NO: 17, and the VL sequence comprises the sequence set forth in SEQ ID NO: 20.
3. The isolated antibody of claim 1, wherein the VH sequence comprises the sequence selected from the sequences set forth in SEQ ID NO: 16, 17, or 18; and the VL sequence comprises the sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22.
4. The isolated antibody of claim 1, wherein the antibody comprises a heavy chain sequence set forth in SEQ ID NO: 34 and a light chain sequence set forth in SEQ ID NO: 35.
5. The isolated antibody of claim 1, wherein the VH sequence consists of the sequence set forth in SEQ ID NO: 17; and the VL sequence consists of the sequence set forth in SEQ ID NO: 20.
6. The isolated antibody of claim 1, wherein the VH sequence consists of the sequence selected from the sequences set forth in SEQ ID NO: 16, 17, or 18; and the VL sequence consists of the sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22.
7. The isolated antibody of claim 1, wherein the antibody consists of the heavy chain sequence set forth in SEQ ID NO: 34 and the light chain sequence set forth in SEQ ID NO: 35.

- 8.** The isolated antibody of claim 1, wherein the antibody is afucosylated, and wherein the VH sequence comprises the sequence set forth in SEQ ID NO: 17, and the VL sequence comprises the sequence set forth in SEQ ID NO: 20.
- 9.** The isolated antibody of claim 1, wherein the antibody is afucosylated, and wherein the VH sequence comprises the sequence selected from the sequences set forth in SEQ ID NO: 16, 17, or 18; and the VL sequence comprises the sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22.
- 10.** The isolated antibody of claim 1, wherein the antibody is afucosylated, and the antibody comprises the heavy chain sequence set forth in SEQ ID NO: 34 and the light chain sequence set forth in SEQ ID NO: 35.
- 11.** The isolated antibody of claim 1, wherein the antibody is afucosylated, and wherein the VH sequence consists of the sequence set forth in SEQ ID NO: 17, and the VL sequence consists of the sequence set forth in SEQ ID NO: 20.
- 12.** The isolated antibody of claim 1, wherein the antibody is afucosylated, and wherein the VH sequence consists of the sequence selected from the sequences set forth in SEQ ID NO: 16, 17, or 18; and the VL sequence consists of the sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22.
- 13.** The isolated antibody of claim 1, wherein the antibody is afucosylated, and the antibody consists of the heavy chain sequence set forth in SEQ ID NO: 34 and the light chain sequence set forth in SEQ ID NO: 35.
- 14.** The isolated antibody of claim 1, wherein the antibody is afucosylated.
- 15.** The isolated antibody of claim 1, wherein the antibody comprises human Fc.
- 16.** The isolated antibody of claim 15, wherein the human Fc is a wild-type human IgG1 Fc.
- 17.** The isolated antibody of claim 1, wherein the antibody is afucosylated and comprises a wild type human IgG1 Fc, and wherein the VH sequence comprises the sequence set forth in SEQ ID NO: 17, and the VL sequence comprises the sequence set forth in SEQ ID NO: 20.
- 18.** The isolated antibody of claim 1, wherein the antibody binds to human TREM1 with a K_D of less than or equal to ~~about~~ 0.5, 1, 2, 3, 4, 5, 6, or 7×10^{-9} M, as measured by surface plasmon resonance (SPR) assay.

19. The isolated antibody of claim 1, wherein the antibody is humanized.
20. A method of producing an antibody comprising expressing the antibody of claim 1 from an isolated host cell and isolating the expressed antibody.
21. A pharmaceutical composition comprising the antibody of claim 1 and a pharmaceutically acceptable excipient.
22. A kit comprising the antibody of claim 1 and instructions for use.
23. An isolated antibody that binds to human TREM1 (SEQ ID NO: 1), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:
 - a. CDR-H1 comprises the sequence set forth in SEQ ID NO: 23,
 - b. CDR-H2 comprises the sequence set forth in SEQ ID NO: 24,
 - c. CDR-H3 comprises the sequence set forth in SEQ ID NO: 32,
 - d. CDR-L1 comprises the sequence set forth in SEQ ID NO: 26,
 - e. CDR-L2 comprises the sequence set forth in SEQ ID NO: 27, and
 - f. CDR-L3 comprises the sequence set forth in SEQ ID NO: 28.
24. The isolated antibody of claim 23, wherein the VH sequence comprises the sequence set forth in SEQ ID NO: 13, and the VL sequence comprises the sequence set forth in SEQ ID NO: 20.
25. A pharmaceutical composition comprising the antibody of claim 23 and a pharmaceutically acceptable excipient.
26. The isolated antibody of claim 23, wherein the VH sequence comprises the sequence selected from the sequences set forth in SEQ ID NO: 12, 13, or 14; and the VL sequence comprises the sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22.
27. A pharmaceutical composition comprising the antibody of claim 2 and a pharmaceutically acceptable excipient.
28. A pharmaceutical composition comprising the antibody of claim 4 and a pharmaceutically acceptable excipient.

- 29.** A pharmaceutical composition comprising the antibody of claim 5 and a pharmaceutically acceptable excipient.
- 30.** A pharmaceutical composition comprising the antibody of claim 7 and a pharmaceutically acceptable excipient.
- 31.** A pharmaceutical composition comprising the antibody of claim 8 and a pharmaceutically acceptable excipient.
- 32.** A pharmaceutical composition comprising the antibody of claim 10 and a pharmaceutically acceptable excipient.
- 33.** A pharmaceutical composition comprising the antibody of claim 11 and a pharmaceutically acceptable excipient.
- 34.** A pharmaceutical composition comprising the antibody of claim 13 and a pharmaceutically acceptable excipient.
- 35.** A pharmaceutical composition comprising the antibody of claim 17 and a pharmaceutically acceptable excipient.
- 36.** The antibody of claim 4, wherein the antibody comprises two heavy chain sequences, each having the sequence as set forth in SEQ ID NO: 34; and two light^s chain sequences, each having the sequence as set forth in SEQ ID NO: 35.
- 37.** The antibody of claim 4, wherein the antibody consists of two heavy chain sequences, each having the sequence as set forth in SEQ ID NO: 34; and two light^s chain sequences, each having the sequence as set forth in SEQ ID NO: 35.
- 38.** The antibody of claim 10, wherein the afucosylated antibody comprises two heavy chain sequences, each having the sequence as set forth in SEQ ID NO: 34; and two light^s chain sequences, each having the sequence as set forth in SEQ ID NO: 35.
- 39.** The antibody of claim 10, wherein the afucosylated antibody consists of two heavy chain sequences, each having the sequence as set forth in SEQ ID NO: 34; and two light^s chain sequences, each having the sequence as set forth in SEQ ID NO: 35.
- 40.** A pharmaceutical composition comprising the antibody of claim 36 and a pharmaceutically acceptable excipient.

- 41.** A pharmaceutical composition comprising the antibody of claim 37 and a pharmaceutically acceptable excipient.
- 42.** A pharmaceutical composition comprising the antibody of claim 38 and a pharmaceutically acceptable excipient.
- 43.** A pharmaceutical composition comprising the antibody of claim 39 and a pharmaceutically acceptable excipient.