from the same subject while being in a different stage of the disease or is determined from clinical data of a large population of subjects.

According to another aspect, the present invention provides an isolated monoclonal antibody which binds to human poliovirus receptor (PVR), or an antibody fragment thereof comprising at least the antigen binding portion, wherein the isolated antibody or antibody fragment comprises:

(i) three complementarity determining regions (CDRs) of a heavy-chain (HC) variable region comprising SEQ ID NO: 77 and three CDRs of a light-chain (LC) variable region comprising SEQ ID NO: 79, or an analog or derivative thereof having at least 90% sequence identity with said antibody or fragment sequence; or

(ii) three CDRs of a heavy-chain variable region comprising SEQ ID NO: 69 and three CDRs of a light-chain variable region comprising SEQ ID NO: 71, or an analog or derivative thereof having at least 90% sequence identity with said antibody or fragment sequence; or

(iii) three CDRs of a heavy-chain variable region comprising SEQ ID NO: 73 and three CDRs of a light-chain variable region comprising SEQ ID NO: 75, or an analog or derivative thereof having at least 90% sequence identity with said antibody or fragment sequence.

According to another aspect, the present invention provides a variant of an isolated monoclonal antibody or antibody fragment as described herein having at least 95% identity with said antibody light or heavy chain.

According to another aspect, the present invention provides a polynucleotide sequence encoding at least one region of a HC or a LC sequence of a monoclonal antibody or antibody fragment as described herein.

According to another aspect, the present invention provides a plasmid comprising at least one polynucleotide sequence as described herein.

According to another aspect, the present invention provides a hybridoma cell comprising a polynucleotide sequence as described herein.

According to another aspect, the present invention provides a hybridoma cell capable of producing a monoclonal antibody as described herein.

According to another aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient, at least one isolated antibody or fragment thereof as described herein, and a pharmaceutical acceptable excipient, diluent, salt or carrier.

According to another aspect, the present invention provides a pharmaceutical composition as described herein for use in modulating the immune system by inhibiting binding of PVR to TIGIT.

According to another aspect, the present invention provides a pharmaceutical composition as described herein for use in treating cancer.

According to another aspect, the present invention provides a pharmaceutical composition as described herein for use in preventing or treating a viral infection in a subject.

According to another aspect, the present invention provides a pharmaceutical composition as described herein for use in treating an angiogenesis-related disease or disorder.

According to another aspect, the present invention provides a use of a pharmaceutical composition as described herein in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a subject in need thereof.

According to another aspect, the present invention provides a method of diagnosing a cancer in a subject, the method comprising contacting a biological sample with an antibody or antibody fragment as described herein.

According to another aspect, the present invention provides a kit for diagnosing a cancer in a subject comprising at least one antibody or antibody fragment as described herein.

Further embodiments and the full scope of applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes

and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1C are graphs depicting the correlation of PVR mRNA expression levels (high or low as indicated) with survival probability. The correlation was measured for lung cancer (Figure 1A), breast cancer (Figure 1B) and liposarcoma (Figure 1C). Data sets of mRNA expression were obtained from the GEO site and analyzed using bioprofiling.de site, as follows: for lung cancer GEO dataset ID: GSE31210, for breast cancer GEO dataset ID: GSE25055 and for liposarcoma GEO dataset ID: GSE30929.

Figure 2 is a schematic illustration of receptor expression on immune and tumor cells. TIGIT relates to a co-inhibitory receptor on many immune cells (e.g. T cells); DNAM-1 (also termed CD226) relates to an activating receptor on many immune cells (e.g. T cells); Fc Receptor relates to the strong activating receptor expressed mainly on NK cells but also on myeloid cells including neutrophils and macrophages; PVR relates to an inhibitory ligand for TIGIT (weaker binding to DNAM-1), expressed by many tumor cells; Nectin-2 relates to an activating ligand for DNAM-1 (marginal recognition by TIGIT), expressed by many tumor cells. Binding of anti-PVR according to the present invention shows a dual effect: 1) enhancing the killing of tumor cells via Fc receptors; and 2) increasing activation of immune cells by blocking the interaction with TIGIT.

Figures 3A-3D. are graphs depicting FACS analysis of the four anti-PVR antibodies generated. Shown is the efficacy of the antibodies in blocking the direct binding of TIGIT-Fc to a tumor cell line. Figure 3A illustrates a non-blocking anti-PVR antibody (anti-PVR mAb antibody 2G3, also termed hPVR.17). Figures 3B-3D show that three of the antibodies generated, namely 5B9 (also termed hPVR.09), 7D4 (also termed hPVR.01) and 4E5 (also termed hPVR.07), respectively, are anti-PVR blocking mAbs as shown by blockage of

NO: 72, SEQ ID NO: 33 and SEQ ID NO: 76, or a variant thereof having at least 90% identity to said sequences.

31. The polynucleotide sequence of claim 29, encoding a monoclonal antibody light chain variable region, wherein the polynucleotide sequence is selected from the group consisting of: SEQ ID NO: 9, SEQ ID NO: 70, SEQ ID NO: 25, SEQ ID NO: 74, SEQ ID NO: 41, and SEQ ID NO: 78, or a variant thereof having at least 90% identity to said sequences.
32. A plasmid comprising at least one polynucleotide sequence according to any one of claims 29 to 31.
33. A hybridoma cell comprising a polynucleotide sequence according to any one of claims 29 to 31.
34. A hybridoma cell capable of producing a monoclonal antibody according to any one of claims 1 to 28.
35. The monoclonal antibody according to any one of claims 1 to 28 attached to a cytotoxic moiety, a radioactive moiety, or an identifiable moiety.
36. A pharmaceutical composition comprising as an active ingredient, at least one isolated antibody or fragment thereof, according to any one of claims 1 to 28 and 35, and a pharmaceutical acceptable excipient, diluent, salt or carrier.
37. The pharmaceutical composition of claim 36 for use in modulating the immune system by inhibiting binding of PVR to TIGIT.
38. The pharmaceutical composition of claim 36 for use in treating cancer.
39. The pharmaceutical composition of claim 36 for use in preventing or treating a viral infection in a subject.
40. The pharmaceutical composition of claim 36 for use in treating an angiogenesis-related disease or disorder.
41. The pharmaceutical composition of claim 40, wherein the angiogenesis-related disease or disorder is selected from the group consisting of: cancer, cell proliferative diseases of the eye, retinal disorders, and inflammatory diseases.
42. Use of a pharmaceutical composition according to claim 36 in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a subject in need thereof.
43. The use of claim 42 further comprising an additional anti-cancer therapy selected from surgery, chemotherapy, radiotherapy, and immunotherapy.

44. The use of claim 42 wherein an additional immuno-modulator, activated lymphocyte cell, kinase inhibitor, chemotherapeutic agent or any other anti-cancer agent is to be further administered to said subject.

45. The use of claim 44, wherein the additional immune-modulator is an antibody against an immune checkpoint molecule selected from the group consisting of PD-1, CTLA-4, PDL-1, CEACAM1, NKG2A, B7-H3, B7-H4, VISTA, CD112R, lymphocyte activation gene 3 (LAG3), CD137, OX40 (also referred to as CD134), killer cell immunoglobulin-like receptors (KIR), TIGIT, and any combination thereof.

46. The use of claim 42, wherein the cancer is a solid cancer.

47. The use of claim 42, wherein the cancer is a hematologic cancer.

48. The use of claim 42, wherein said use results in preventing or reducing metastases formation, growth or spread in a subject.

49. A method of diagnosing a cancer in a subject, the method comprising contacting a biological sample with an antibody or antibody fragment according to any one of claims 1 to 28.

50. A kit for diagnosing a cancer in a subject comprising at least one antibody or antibody fragment according to any one of claims 1 to 28.