

binds with high affinity to polio virus receptor (PVR, CD155) and with low affinity to Nectin-2 (CD112), both expressed by various cancer cells.

CD112R, also called PVRIG, binds with high affinity to Nectin-2. Upon interaction with CD112R, and/or TIGIT, Nectin-2 inhibits T-cell proliferation. Importantly, Nectin-2 can also serve as a costimulator of T-cell functions, upon binding to CD226 (DNAM-1). This interaction stimulates T-cell proliferation and cytokine production, such as IL-2, and IFN γ . These contradictory interactions are competitive, and their net effect impacts the resulting anti-cancer immune response.

WO2019232484 discloses anti-PVRIG, anti-TIGIT, and anti-PVRIG/anti-TIGIT bispecific antibodies, as well as compositions, and methods of using the antibodies for the treatment of cancer.

WO2018017864 discloses agents and bi-specific agents, including antibodies that specifically bind PVRIG. WO2018017864 also discloses methods of using the agents for enhancing the immune response and/or treatment of diseases such as cancer.

WO2016134333 discloses anti-PVRIG antibodies and methods of using same.

There is an unmet need for additional and more effective, specific, safe, and stable agents that alone, or in combination with other agents, may potentiate cells of the immune system to attack tumors or virus infected cells. Monoclonal antibodies (mAbs) inhibiting CD112R binding to Nectin-2, may be such agents.

SUMMARY OF THE INVENTION

The present invention provides an antibody that binds to CD112R, or an antibody fragment thereof, comprising at least the antigen binding portion, wherein the antibody or antibody fragment comprises a set of six CDRs wherein: heavy chain CDR1 sequence comprising the sequence GYX1FX2SY (SEQ ID NO: 1), wherein X1 denotes N, D, A, Q, S, or T, and X2 is T or A, or the sequence SYWIN (SEQ ID NO: 7), heavy chain CDR2 comprising the sequence YPGSYIP (SEQ ID NO: 2) or FPGSYS (SEQ ID NO: 10), heavy chain CDR3 comprising the sequence GYFDV (SEQ ID NO: 3), light chain CDR1 comprising the sequence KSSQSLXSGNQKNYLA (SEQ ID NO: 4), wherein X denotes N or S, light chain CDR2 comprising the sequence GASTRES (SEQ ID NO: 5), and light chain CDR3 comprising the sequence QNDHSYPYT (SEQ ID NO: 6).

The present invention provides an antibody fragment as described herein, wherein the antibody fragment is a single chain Fv (scFv).

The present invention provides a polypeptide comprising a scFv as described herein and a human IgG1 Fc region sequence, wherein the polypeptide comprises a sequence set forth in any one of SEQ ID NOs: 43 to 54, or an analog or derivative thereof having at least 90% sequence identity to said polypeptide.

The present invention provides an antibody or antibody fragment as described herein, wherein the antibody binds to human CD112R with an affinity of at least $1 \times 10^{-9} \text{M}$.

The present invention provides a polynucleotide sequence encoding at least one sequence of a heavy chain or a light chain region of an antibody or antibody fragment as described herein.

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

The present invention provides the use of the pharmaceutical composition as described herein in the manufacture of a medicament for modulating the immune system, wherein the medicament inhibits the binding of CD112R to Nectin-2.

The present invention provides the use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating cancer in a subject.

The present invention provides the use of the pharmaceutical composition as described herein in the manufacture of a medicament for preventing or treating a viral infection in a subject.

The present invention provides a method of diagnosing or prognosing cancer in a subject, the method comprises determining the expression level of CD112R in a biological sample obtained from said subject using at least one antibody or antibody fragment as described herein.

The present invention provides a pharmaceutical composition as described herein for use in therapy.

The present invention provides antibodies and fragments thereof that recognize CD112R (PVRIG), bind it, prevent its binding to Nectin-2 (CD112) and inhibit the resulting suppressive

activity on lymphocytes such as natural killer (NK) cells and T-cells. These antibodies and fragment thereof are characterized by having unique sets of CDR sequences, high affinity, and high specificity to human CD112R, and are useful in cancer immunotherapy for combating tumor immune evasion, as either a stand-alone therapy or in combination with other anti-cancer agents. The antibodies disclosed herein are also useful in treating viral infections and may be used for detection assays and cancer diagnosis.

anti-CD112R mAb, or with anti-PD-1 mAb (Pembrolizumab), once weekly at 10 mg/kg for a total of 5 doses. Tumor volume was measured once weekly by a caliper. On day 35 the average tumor volume of the control IgG treated group was 641mm³ and the tumor volume of the anti PD-1 treated group was 840 mm³ (Fig. 12). These results were not significantly different by two-way-ANOVA. On the other hand, the average volume of the anti CD112R-treated tumors was 200 mm³, representing 68% tumor growth inhibition, and significant tumor reduction compared to IgG treated animals (***p=0.001 by two-way ANOVA).

Example 17. Antibody sequences

Table 10: details of CDR sequences, variable regions sequences of the different clones and variant thereof, and scFv sequences.

	Amino acid SEQ ID Nos:	Nucleotide SEQ ID Nos:
Clone 13 and variants		
HC CDR1	1, 7	
HC CDR2	2, 8	
HC CDR3	3	
LC CDR1	4	
LC CDR2	5	
LC CDR3	6	
HC variable region	17	16, 24
LC variable region	19	18, 25
LC CDR1—wherein X= N (deamidation site) or S	26	
LC CDR1—wherein N31S (deamidation removal)	27	
HC CDR1—wherein N-Linked glycosylation site X ₁ = N (parental), D, A, Q, S, or T; X ₂ =T (parental) or A	28	
HC variant 1 (H1)	29	
HC variant 2 (H2)	30	
HC variant 3 (H3)	31	
HC variant 4 (H4)	32	
HC variant 5 (H5)	33	
HC variant 6 (H6)	34	
HC variant 7 (H7)	35	
HC variant 8 (H8)	36	
HC variant 9 (H9)	37	
HC variant 10 (H10)	38	
HC variant 11 (H11)	39	
LC variant 1 (K1)	40	
LC variant 2 (K2)	41	
LC variant 3 (K3)	42	
scFv variants connected to hIgG1		

Variant_0	43	
Variant 1 N28T LC	44	
Variants_2-11	45-54	
Clone 15		
HC CDR1	9, 7	
HC CDR2	10, 12	
HC CDR3	3	
LC CDR1	11	
LC CDR2	5	
LC CDR3	6	
HC variable region	2021	2120
LV variable region	2223	2322

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without undue experimentation and without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation.