

Claims

1. A single domain antibody (sdAb) which specifically binds to Leukocyte immunoglobulin-like receptor subfamily B member 2 (LILRB2), ~~preferably human LILRB2.~~

2. The single domain antibody (sdAb) of claim 1, wherein the sdAb specifically binds to human LILRB2.

~~3. The sdAb according to claim 1, wherein said sdAb does not bind Leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1), preferably human LILRB1.~~

4. The single domain antibody (sdAb) of any one of claims 1-9 or 18, wherein the sdAb specifically binds to human LILRB1.

~~35. The sdAb according to any one of claims 1 to 4 or 2, wherein said sdAb comprises at least one complementarity determining regions (CDR) which comprises or consists in the sequence set forth in SEQ ID NO: 3, 6, 9, 12, 15, 18, 21, 24, 27, 30 or 33 or comprises, or consists in an amino acid sequence which differs from SEQ ID NO: 3, 6, 9, 12, 15, 18, 21, 24, 27, 30 or 33 in virtue of one, two, or three amino acid modifications.~~

46. The sdAb according to any of claims 1 to ~~35~~, wherein said sdAb comprises three CDRs, wherein:

(a) CDR1 comprises, or is of, SEQ ID NO:1 or has an amino acid sequence which differs from SEQ ID NO:1 in virtue of one, two, or three amino acid modifications, and
CDR2 comprises, or is of, SEQ ID NO:2 or has an amino acid sequence which differs from SEQ ID NO:2 in virtue of one, two, or three amino acid modifications, and
CDR3 comprises, or is of, SEQ ID NO:3 or has an amino acid sequence which differs from SEQ ID NO:3 in virtue of one, two, three or four amino acid modifications; or

(b) CDR1 comprises, or is of, SEQ ID NO:4 or has an amino acid sequence which differs from SEQ ID NO:4 in virtue of one, two, or three amino acid modifications, and
CDR2 comprises, or is of, SEQ ID NO:5 or has an amino acid sequence which differs from SEQ ID NO:5 in virtue of one, two, or three amino acid modifications, and
CDR3 comprises, or is of, SEQ ID NO:6 or has an amino acid sequence which differs from SEQ ID NO:6 in virtue of one, two, three or four amino acid modifications; or

(c) CDR1 comprises, or is of, SEQ ID NO:7 or has an amino acid sequence which differs from SEQ ID NO:7 in virtue of one, two, or three amino acid modifications, and
CDR2 comprises, or is of, SEQ ID NO:8 or has an amino acid sequence which differs from SEQ ID NO:8 in virtue of one, two, or three amino acid modifications, and
CDR3 comprises, or is of, SEQ ID NO:9 or has an amino acid sequence which differs from SEQ ID NO:9 in virtue of one, two, three or four amino acid modifications; or

- (d) CDR1 comprises, or is of, SEQ ID NO:10 or has an amino acid sequence which differs from SEQ ID NO:10 in virtue of one, two, or three amino acid modifications, and
 CDR2 comprises, or is of, SEQ ID NO:11 or has an amino acid sequence which differs from SEQ ID NO:11 in virtue of one, two, or three amino acid modifications, and
 5 CDR3 comprises, or is of, SEQ ID NO:12 or has an amino acid sequence which differs from SEQ ID NO:12 in virtue of one, two, three or four amino acid modifications; or
- (e) CDR1 comprises, or is of, SEQ ID NO:13 or has an amino acid sequence which differs from SEQ ID NO:13 in virtue of one, two, or three amino acid modifications, and
 CDR2 comprises, or is of, SEQ ID NO:14 or has an amino acid sequence which differs from SEQ ID
 10 NO:14 in virtue of one, two, or three amino acid modifications, and
 CDR3 comprises, or is of, SEQ ID NO:15 or has an amino acid sequence which differs from SEQ ID NO:15 in virtue of one, two, three or four amino acid modifications; or
- (f) CDR1 comprises, or is of, SEQ ID NO:16 or has an amino acid sequence which differs from SEQ ID NO:16 in virtue of one, two, or three amino acid modifications, and
 15 CDR2 comprises, or is of, SEQ ID NO:17 or has an amino acid sequence which differs from SEQ ID NO:17 in virtue of one, two, or three amino acid modifications, and
 CDR3 comprises, or is of, SEQ ID NO:18 or has an amino acid sequence which differs from SEQ ID NO:18 in virtue of one, two, three or four amino acid modifications; or
- (g) CDR1 comprises, or is of, SEQ ID NO:19 or has an amino acid sequence which differs from SEQ ID
 20 NO:19 in virtue of one, two, or three amino acid modifications, and
 CDR2 comprises, or is of, SEQ ID NO:20 or has an amino acid sequence which differs from SEQ ID NO:20 in virtue of one, two, or three amino acid modifications, and
 CDR3 comprises, or is of, SEQ ID NO:21 or has an amino acid sequence which differs from SEQ ID NO:21 in virtue of one, two, three or four amino acid modifications; or
- (h) CDR1 comprises, or is of, SEQ ID NO:22 or has an amino acid sequence which differs from SEQ ID
 25 NO:22 in virtue of one, two, or three amino acid modifications, and
 CDR2 comprises, or is of, SEQ ID NO:23 or has an amino acid sequence which differs from SEQ ID NO:23 in virtue of one, two, or three amino acid modifications, and
 CDR3 comprises, or is of, SEQ ID NO:24 or has an amino acid sequence which differs from SEQ ID
 30 NO:24 in virtue of one, two, three or four amino acid modifications; or
- (i) CDR1 comprises, or is of, SEQ ID NO:25 or has an amino acid sequence which differs from SEQ ID NO:25 in virtue of one, two, or three amino acid modifications, and
 CDR2 comprises, or is of, SEQ ID NO:26 or has an amino acid sequence which differs from SEQ ID NO:26 in virtue of one, two, or three amino acid modifications, and
 35 CDR3 comprises, or is of, SEQ ID NO:27 or has an amino acid sequence which differs from SEQ ID NO:27 in virtue of one, two, three or four amino acid modifications; or

- (j) CDR1 comprises, or is of, SEQ ID NO:28 or has an amino acid sequence which differs from SEQ ID NO:28 in virtue of one, two, or three amino acid modifications, and CDR2 comprises, or is of, SEQ ID NO:29 or has an amino acid sequence which differs from SEQ ID NO:29 in virtue of one, two, or three amino acid modifications, and
- 5 CDR3 comprises, or is of, SEQ ID NO:30 or has an amino acid sequence which differs from SEQ ID NO:30 in virtue of one, two, three or four amino acid modifications; or
- (k) CDR1 comprises, or is of, SEQ ID NO:31 or has an amino acid sequence which differs from SEQ ID NO:31 in virtue of one, two, or three amino acid modifications, and CDR2 comprises, or is of, SEQ ID NO:32 or has an amino acid sequence which differs from SEQ ID
- 10 NO: 32 in virtue of one, two, or three amino acid modifications, and CDR3 comprises, or is of, SEQ ID NO:33 or has an amino acid sequence which differs from SEQ ID NO:33 in virtue of one, two, three or four amino acid modifications.

57. The sdAb according to any of claims 1 to 35, wherein said sdAb comprises three CDRs, wherein CDR1 comprises or consists of SEQ ID NO:1, and CDR2 comprises or consists of SEQ ID NO:2, and

15 CDR3 comprises or consists of SEQ ID NO:3.

68. The sdAb according to any of claims 1 to 57, which comprises or consists in a sequence defined in any of the sequence SEQ ID No: 34 to SEQ ID No: 44 or a sequence having at least 80% sequence identity thereto, ~~preferably at least 90%, 92%, 94%, 95%, 96%, 97%, 98%, 99% or more amino-acid sequence identity thereto.~~

9. The sdAb according to any of claims 1 to 8, which comprises or consists in a sequence defined in any of the sequence SEQ ID No: 34 to SEQ ID No: 44 or a sequence having at least 90%, 92%, 94%, 95%, 96%, 97%, 98%, 99% or more amino-acid sequence identity thereto.

710. The sdAb according to any of claims 1 to 59, which comprises or consists in a sequence defined in SEQ ID No: 34.

811. The sdAb according to any of claims 1 to 710, wherein said sdAb inhibits the interaction between LILRB2 and human leukocyte antigen-G (HLA-G).

912. The sdAb according to any of claims 1 to 811, wherein said sdAb inhibits the interaction between LILRB2 and Angiopoietin Like 2 (ANGPTL2).

1013. ~~An isolated nucleic acid comprising a sequence encoding a sdAb as defined in any one of claims 1 to 912 preferably defined by a sequence selected in the group consisting of SEQ ID: 45-55.~~

14. The isolated nucleic acid according to claim 13, wherein the nucleic acid comprises a sequence encoding a sdAb as defined by a sequence selected in the group consisting of SEQ ID: 45-55.

~~11~~15. A vector comprising the isolated nucleic acid of claim ~~10~~13 or 14.

~~12~~16. A chimeric antigen receptor (CAR) comprising the sdAb according to any one of claims ~~1-9~~1-12 or the isolated nucleic acid of claims ~~8~~13-14.

~~13~~17. A cell comprising the isolated nucleic acid of claim ~~10~~13-14, or the vector of claim ~~11~~15, or expressing the CAR of claim ~~12~~16.

~~14~~18. The cell expressing a CAR according to claim ~~13~~17, wherein the cell is selected from a group consisting of a T cell, CD4⁺ T cell, CD8⁺ T cell, B cell, NK cell, NKT cell, monocyte and dendritic cell, ~~preferably the cell being a T cell, a B cell or a NK cell.~~

19. The cell according to claim 18, wherein the cell is selected from a T cell, a B cell or a NK cell.

~~15~~20. A pharmaceutical composition comprising a sdAb as defined in any one of claims ~~1-7~~1-12, the isolated nucleic acid of claim ~~10~~13-14, the vector of claim ~~11~~15, the CAR or claim ~~12-16~~ or the cell expressing a CAR according to any claims 17 to 19-13 or 14, and optionally a pharmaceutically acceptable carrier.

~~16~~21. The sdAb of any one of claims claim ~~1-9~~1-12, the isolated nucleic acid of any claims 1013-14, the vector of claim ~~11~~15, the CAR of claim ~~12~~16, the cell of any one of claims ~~13-14~~17-19 or the pharmaceutical composition of claim ~~15~~20, for use in the treatment of cancer, ~~preferably wherein the cancer overexpresses LILBR2 more preferably a cancer selected from the group consisting of lung cancer, non-small cell lung cancer (NSCLC), pancreatic cancer, pancreatic ductal carcinoma, Chronic Lymphocytic Leukemia (CLL), Acute Myeloid Leukemia (AML), endometrial cancer, hepatocellular carcinoma, melanoma, ovarian cancer, breast cancer, colorectal cancer, glioma, stomach cancer, renal cancer, testis cancer, Esophageal cancer, Cervical cancer, Lewis Lung cancer of mice, Leukemia, Thyroid cancer, Liver cancer, Urothelial cancer and Head and neck cancer.~~

22. Use of the sdAb of any one of claims ~~1-12~~, the isolated nucleic acid of any of claims ~~13-14~~, the vector of claim 15, the CAR of claim 16, the cell of any one of claims ~~17-19~~ or the pharmaceutical composition of claim 20, in the preparation of a medicament for treating cancer.

23 The sdAb, the isolated nucleic acid, the vector, the CAR, the cell, or the pharmaceutical composition, according to claim 21, or the use according to claim 22, wherein the cancer overexpresses LILBR2.

24. The sdAb, the isolated nucleic acid, the vector, the CAR, the cell, or the pharmaceutical composition, according to claim 21, or the use according to claim 22, wherein the cancer is selected from the group consisting of lung cancer, non-small cell lung cancer (NSCLC), pancreatic cancer, pancreatic ductal carcinoma, Chronic Lymphocytic Leukemia (CLL), Acute Myeloid Leukemia (AML), endometrial cancer, hepatocellular carcinoma, melanoma, ovarian cancer,

breast cancer, colorectal cancer, glioma, stomach cancer, renal cancer, testis cancer, Esophageal cancer, Cervical cancer, Lewis Lung cancer of mice, Leukemia, Thyroid cancer, Liver cancer, Urothelial cancer and Head and neck cancer.

1725. Use of the sdAb of any one of claims claim 1-912, for detecting LILRB2 on tumoral cells or tissues *in vitro* or *ex vivo*.