

what is claimed is:

1. A chimeric antigen receptor (CAR) comprising a DLL3 binding domain, wherein the DLL3 binding domain comprises or is derived from a single domain antibody (sdAb) or a single chain variable fragment (scFv).

2. The CAR as claimed in claim 1, wherein the sdAb comprises a polypeptide that comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-81 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1, a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 82-162 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2, and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 163-243 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3.

3. The CAR as claimed in claim 1 or claim 2, wherein the sdAb comprises a polypeptide that comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-81, a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 82-162 and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 163-243, or a variant of the polypeptide comprising up to about 3 amino acid substitutions in the CDR1, CDR2 and CDR3.

4. The CAR as claimed in any one of claims 1-3, wherein the sdAb comprises a polypeptide comprising any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 87, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 168, or a variant thereof comprising up to about 3 amino acid substitutions;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 21, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof comprising up to about 3 amino acid substitutions;

(3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 105, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 186, or a variant thereof comprising up to about 3 amino acid substitutions;

(4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 27, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 108, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189, or a variant thereof comprising up to about 3 amino acid substitutions;

(5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ

ID NO: 196, or a variant thereof comprising up to about 3 amino acid substitutions;

(6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 201, or a variant thereof comprising up to about 3 amino acid substitutions;

(7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 7, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 88, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 169, or a variant thereof comprising up to about 3 amino acid substitutions;

(8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 89, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 170, or a variant thereof comprising up to about 3 amino acid substitutions; or

(9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 9, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 90, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 171, or a variant thereof comprising up to about 3 amino acid substitutions.

5. The CAR as claimed in any one of claims 1-4, wherein the sdAb comprises a polypeptide comprising any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 6; a CDR2 comprising the amino acid sequence of SEQ ID NO: 87; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 168;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 21; a CDR2 comprising the amino acid sequence of SEQ ID NO: 102; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 183;

(3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24; a CDR2 comprising the amino acid sequence of SEQ ID NO: 105; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 186;

(4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 27; a CDR2 comprising the amino acid sequence of SEQ ID NO: 108; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189;

(5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 34; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 115; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 196;

(6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 201;

(7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 7; a CDR2 comprising the amino acid sequence of SEQ ID NO: 88; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 169;

(8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 8; a CDR2 comprising the amino acid sequence of SEQ ID NO: 89; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 170; or

(9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 9; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 90; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 171.

6. The CAR as claimed in any one of claims 1-5, wherein the sdAb is a camel sdAb raised against human or rhesus DLL3.

7. The CAR as claimed in any one of claims 1-6, wherein the sdAb comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 274-354.

8. The CAR as claimed in any one of claims 1-7, wherein the sdAb is humanized through CDR grafting.

9. The CAR as claimed in any one of claims 1-8, wherein the humanized sdAb comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 355-367.

10. The CAR as claimed in any one of claims 1-9, wherein the scFv comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH of the scFv comprises a CDR1 set forth in SEQ ID NO: 498 or 504 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1, a CDR2 set forth in SEQ ID NO: 499 or 505 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2, and a CDR3 set forth in SEQ ID NO: 500 or 506 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3, and the VL of the scFv comprises a CDR1 set forth in SEQ ID NO: 495 or 501 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1, a CDR2 set forth in SEQ ID NO: 496 or 502 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2, and a CDR3 set forth in SEQ ID NO: 497 or 503 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3.

11. The CAR as claimed in any one of claims 1-10, wherein the VH of the scFv comprises a CDR1 set forth in SEQ ID NO: 498, a CDR2 set forth in SEQ ID NO: 499, and a CDR3 set forth in SEQ ID NO: 500, and the VL of the scFv comprises a CDR1 set forth in SEQ ID NO: 495, a CDR2 set forth in SEQ ID NO: 496, and a CDR3 set forth in SEQ ID NO: 497; or the VH of the scFv comprises a CDR1 set forth in SEQ ID NO: 504, a CDR2 set forth in SEQ ID NO: 505, and a CDR3 set forth in SEQ ID NO: 506, and the VL of the scFv comprises a CDR1 set forth in SEQ ID NO: 501, a CDR2 set forth in SEQ ID NO: 502, and a CDR3 set forth in SEQ ID NO: 503.

12. The CAR as claimed in any one of claims 1-11, the VH of the scFv comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 508, and the VL of the scFv comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 507; or the VH of the scFv comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence

set forth in SEQ ID NO: 510, and the VL of the scFv comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 509.

13. The CAR as claimed in any one of claims 1-12, wherein the scFv is obtained from a synthetic human Fab phage library.

14. The CAR as claimed in any one of claims 1-13, wherein the DLL3 is human or rhesus DLL3.

15. The CAR as claimed in any one of claims 1-14, wherein the CAR comprises, from N-terminus to C-terminus, a signal peptide, the DLL3 binding domain, a hinge domain, a transmembrane domain, and an intracellular signaling domain.

16. The CAR as claimed in any one of claims 1-15, wherein the intracellular signaling domain is derived from CD3 ζ , FcR γ , FcR β , CD3 γ , CD3 δ , CD3 ϵ , CD5, CD22, CD79a, CD79b, or CD66d.

17. The CAR as claimed in any one of claims 1-16, wherein the intracellular signaling domain further comprises an intracellular co-stimulatory sequence.

18. The CAR as claimed in any one of claims 1-17, wherein the intracellular co-stimulatory sequence is derived from a co-stimulatory molecule selected from the group consisting of CD27, CD28, 4-1BB, OX40, CD40, PD-1, LFA-1, ICOS, CD2, CD7, LIGHT, NKG2C, B7-H3, TNFRSF9, TNFRSF4, TNFRSF8, CD40LG, ITGB2, KLRC2, TNFRSF18, TNFRSF14, HAVCR1, LGALS9, DAP10, DAP12, CD83, ligands of CD83 and combinations thereof.

19. The CAR as claimed in any one of claims 1-18, wherein the CAR comprises an amino acid sequence having at least about 95% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 476-484, SEQ ID NOs: 485-494, or SEQ ID NOs:515-516.

20. The CAR as claimed in any one of claims 1-19, wherein the DLL3 binding domain comprises two sdAbs linked to each other.

21. The CAR as claimed in any one of claims 1-20, wherein the each of the sdAbs independently comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO:356 or SEQ ID NO:366.

22. The CAR as claimed in any one of claims 1-21, wherein the CAR comprises an amino acid sequence having at least about 95% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 518-520.

23. The CAR as claimed in any one of claims 1-22, wherein the CAR comprises an amino acid sequence of SEQ ID NO: 520.

24. A DLL3 binding protein comprising a single domain antibody (sdAb) moiety that specifically binds to DLL3, wherein the sdAb moiety comprises a polypeptide that comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-81 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1, a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 82-162 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2, and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 163-243 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3.

25. The DLL3 binding protein of claim 24, wherein the sdAb moiety comprises a polypeptide that comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-81, a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 82-162 and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 163-243, or a variant of the polypeptide comprising up to about 3 amino acid substitutions in the CDR1, CDR2 and CDR3.

26. The DLL3 binding protein as claimed in claim 24 or claim 25, wherein the sdAb moiety comprises a polypeptide comprising any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 87, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 168, or a variant thereof comprising up to about 3 amino acid substitutions;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 21, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof comprising up to about 3 amino acid substitutions;

(3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 105, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 186, or a variant thereof comprising up to about 3 amino acid substitutions;

(4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 27, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 108, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189, or a variant thereof comprising up to about 3 amino acid substitutions;

(5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 196, or a variant thereof comprising up to about 3 amino acid substitutions;

(6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 201, or a variant thereof comprising up to about 3 amino acid substitutions;

(7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 7, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 88, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 169, or a variant thereof comprising up to about 3 amino acid substitutions;

(8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 8, or a variant

thereof comprising up to about 3 amino acid substitutions; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 89, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 170, or a variant thereof comprising up to about 3 amino acid substitutions; or

(9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 9, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 90, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 171, or a variant thereof comprising up to about 3 amino acid substitutions.

27. The DLL3 binding protein as claimed in any one of claims 24-26, wherein the sdAb moiety comprises a polypeptide comprising any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 6; a CDR2 comprising the amino acid sequence of SEQ ID NO: 87; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 168;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 21; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 102; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 183;

(3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24; a CDR2 comprising the amino acid sequence of SEQ ID NO: 105; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 186;

(4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 27; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 108; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189;

(5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 34; a CDR2 comprising the amino acid sequence of SEQ ID NO: 115; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 196;

(6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 201;

(7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 7; a CDR2 comprising the amino acid sequence of SEQ ID NO: 88; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 169;

(8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 8; a CDR2 comprising the amino acid sequence of SEQ ID NO: 89; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 170; or

(9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 9; a CDR2 comprising the amino acid sequence of SEQ ID NO: 90; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 171.

28. The DLL3 binding protein as claimed in any one of claims 24-27, wherein the sdAb moiety is a camel sdAb raised against human or rhesus DLL3.

29. The DLL3 binding protein as claimed in any one of claims 24-28, wherein the sdAb moiety comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 274-354.

30. The DLL3 binding protein as claimed in any one of claims 24-29, wherein

the sdAb moiety is humanized through CDR grafting.

31. The DLL3 binding protein as claimed in any one of claims 24-30, wherein the humanized sdAb comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 355- 367.

32. The DLL3 binding protein as claimed in any one of claims 24-31, wherein the DLL3 is human or rhesus DLL3.

33. A DLL3 binding protein comprising a single chain variable fragment (scFv) moiety that specifically binds to DLL3, wherein the scFv moiety comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH of the scFv moiety comprises a CDR1 set forth in SEQ ID NO: 498 or 504 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1, a CDR2 set forth in SEQ ID NO: 499 or 505 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2, and a CDR3 set forth in SEQ ID NO: 500 or 506 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3, and the VL of the scFv moiety comprises a CDR1 set forth in SEQ ID NO: 495 or 501 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1, a CDR2 set forth in SEQ ID NO: 496 or 502 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2, and a CDR3 set forth in SEQ ID NO: 497 or 503 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3.

34. The DLL3 binding protein as claimed in claim 33, wherein the VH of the scFv moiety comprises a CDR1 set forth in SEQ ID NO: 498, a CDR2 set forth in SEQ ID NO: 499, and a CDR3 set forth in SEQ ID NO: 500, and the VL of the scFv moiety comprises a CDR1 set forth in SEQ ID NO: 495, a CDR2 set forth in SEQ ID NO: 496, and a CDR3 set forth in SEQ ID NO: 497; or the VH of the scFv moiety comprises a CDR1 set forth in SEQ ID NO: 504, a CDR2 set forth in SEQ ID NO: 505, and a CDR3 set forth in SEQ ID NO: 506, and the VL of the scFv moiety comprises a CDR1 set forth in SEQ ID NO: 501, a CDR2 set forth in SEQ ID NO: 502, and a CDR3 set forth in SEQ ID NO: 503.

35. The DLL3 binding protein as claimed in claim 33 or claim 34, wherein the VH of the scFv moiety comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 508, and the VL of the scFv moiety comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 507; or the VH of the scFv moiety comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 510, and the VL of the scFv moiety comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 509.

36. The DLL3 binding protein as claimed in any one of claims 33-35, wherein the scFv moiety is obtained from a synthetic human Fab phage library.

37. The DLL3 binding protein as claimed in any one of claims 33-36, wherein the DLL3 is human or rhesus DLL3.

38. An isolated nucleic acid molecule encoding a CAR as claimed in any of claims 1-23 or an DLL3 binding protein as claimed in any one of claims 24-32 or

claims 33-37.

39. The isolated nucleic acid molecule as claimed in claim 38, wherein the isolated nucleic acid molecule comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOs: 368-448 which encodes a camel single domain antibody (sdAb).

40. The isolated nucleic acid molecule as claimed in claim 38 or claim 39, wherein the isolated nucleic acid molecule comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOs: 449-461 which encodes a humanized camel sdAb.

41. The isolated nucleic acid molecule as claimed in any one of claims 38-40, wherein the nucleic acid molecule comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOs: 511-514 which encodes a VL or VH domain of a human scFv.

42. The isolated nucleic acid molecule as claimed in any one of claims 38-41, wherein the nucleic acid molecule further comprises a polynucleotide sequence encoding a Chimeric Switch Receptor (CSR) or a Dominant Negative Receptor (DNR).

43. The isolated nucleic acid molecule as claimed in any one of claims 38-42, wherein the nucleic acid molecule further comprises a polynucleotide sequence encoding a PD-1 Dominant Negative Receptor (PD-1 DNR), a PD-1 Chimeric Switch Receptor (PD-1 CSR), or a TGF- β Dominant Negative Receptor (TGF- β DNR).

44. The isolated nucleic acid molecule as claimed in any one of claims 38-43, wherein the PD-1 DNR comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO: 523; the PD-1 CSR comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO: 524.

45. The isolated nucleic acid molecule as claimed in any one of claims 38-44, wherein the TGF- β DNR comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO: 529.

46. The isolated nucleic acid molecule as claimed in any one of claims 38-45, wherein the polynucleotide sequence encoding the PD-1 DNR, the PD-1 CSR or the TGF- β DNR is linked to the polynucleotide sequence encoding the CAR through a polynucleotide sequence encoding a 2A self-cleaving peptide.

47. The isolated nucleic acid molecule as claimed in any one of claims 38-46, wherein the 2A self-cleaving peptide is a T2A peptide or a P2A peptide.

48. The isolated nucleic acid molecule as claimed in any one of claims 38-47, wherein the nucleic acid molecule comprises, in the 5' to 3' direction, a polynucleotide sequence encoding the CAR, a polynucleotide sequence encoding the 2A self-cleaving peptide, and a polynucleotide sequence encoding the PD-1 DNR, the PD-1 CSR or the TGF- β DNR.

49. The isolated nucleic acid molecule as claimed in any one of claims 38-48, wherein the nucleic acid molecule encoding a peptide having at least about 95% sequence identity to SEQ ID NO: 521 or 522, or the nucleic acid molecule encoding a peptide having at least about 95% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 525-528.

50. An expression vector comprising an isolated nucleic acid molecule as claimed in any one of claims 38-49.

51. An engineered immune cell comprising an isolated nucleic acid molecule as claimed in any one of claims 38-49 or an expression vector as claimed in claim 50.

52. The engineered immune cell according to claim 51, wherein the engineered immune cell is selected from the group consisting of a cytotoxic T cell, a helper T cell, a natural killer T cell, a $\gamma\delta$ T cell, a NKT cell and a Nature Killer cell.

53. An engineered immune cell expressing a CAR as claimed in any one of claims 1-23.

54. The engineered immune cell according to claim 53, wherein the engineered immune cell also expresses a CSR or a DNR.

55. The engineered immune cell according to claim 53 or claim 54, wherein the CSR is a PD-1 CSR, the DNR is a PD-1 DNR or a TGF- β DNR.

56. The engineered immune cell according to any one of claims 53-55, wherein the PD-1 DNR comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO: 523; the PD-1 CSR comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO: 524.

57. The engineered immune cell according to any one of claims 53-56, wherein the TGF- β DNR comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO: 529.

58. The engineered immune cell according to any one of claims 53-57, wherein the CAR and the CSR, or the CAR and the DNR, are co-expressed through a 2A self-cleaving peptide.

59. The engineered immune cell according to any one of claims 53-58, wherein the 2A self-cleaving peptide is a T2A peptide or a P2A peptide.

60. The engineered immune cell according to any one of claims 53-59, wherein the engineered immune cell expresses the CAR and the PD-1 CSR,

61. The engineered immune cell according to any one of claims 53-60, wherein the engineered immune cell expresses the CAR and the TGF- β DNR, and is stimulated by a cell expressing DLL3 in the present of TGF- β .

62. The engineered immune cell according to any one of claims 53-61, wherein the engineered immune cell is selected from the group consisting of a cytotoxic T cell, a helper T cell, a natural killer T cell, a $\gamma\delta$ T cell, a NKT cell and a Nature Killer cell.

63. A pharmaceutical composition comprising a CAR as claimed in any one of claims 1-23, a DLL3 binding protein as claimed in any one of claims 24-32 or claims 33-37, an expression vector as claimed in claim 50, or an engineered immune cell as claimed in any one of claims 51-62, and a physiologically acceptable excipient.

64. A method for treating a DLL3 associated disorder in a subject, comprising administering to the subject a therapeutically effective amount of engineered immune cells as claimed in any one of claims 51-62 or a therapeutically effective amount of a pharmaceutical composition as claimed in claim 63.

65. The method as claimed in claim 64, wherein the DLL3 associated disorder is a cancer selected from the group consisting of lung cancer, melanoma, breast cancer, prostate cancer, colon cancer, renal cell carcinoma,

ovarian cancer, neuroblastoma, rhabdomyosarcoma, leukemia and lymphoma.

66. The method as claimed in claim 65, wherein the DLL3 associated disorder is small cell lung cancer.

67. The method as claimed in any one of claims 64-66, wherein the cancer expresses DLL3 and PD-L1.

68. The method as claimed in any one of claims 64-67, wherein the cancer has a higher expression level of TGF- β compared to corresponding normal tissue.

69. Use of a CAR as claimed in any one of claims 1-23, an DLL3 binding protein as claimed in any one of claims 24-32 or claims 33-37, an expression vector as claimed in claim 50, or an engineer immune cell as claimed in any one of claims 51-62 for the preparation of a medicament for treating a DLL3 associated disorder.

70. A medicament for use in treating a DLL3 associated disorder comprising a CAR as claimed in any one of claims 1-23, a DLL3 binding protein as claimed in any one of claims 24-32 or claims 33-37, an expression vector as claimed in claim 50, or an engineered immune cell as claimed in any one of claims 51-62.