

CLAIMS:

1. A chimeric antigen receptor including an antigen-recognition domain recognising a dysfunctional P2X7 receptor, a transmembrane domain and a linker domain, wherein the linker domain consists of between 12 to 228 amino acids.
2. The chimeric antigen receptor according to claim 1, where in the linker domain consists of between 30 to 228 amino acids.
3. The chimeric antigen receptor according to claim 1, wherein the linker domain consists of 50 to 200 amino acids.
4. The chimeric antigen receptor according to claim 1, wherein the linker domain consists of 70 to 180 amino acids.
5. The chimeric antigen receptor according to claim 1, wherein the linker domain consists of 90 to 160 amino acids.
6. The chimeric antigen receptor according to claim 1, wherein the linker domain consists of 110 to 130 amino acids.
7. The chimeric antigen receptor according to claim 1, wherein the linker domain consists of 115 to 125 amino acids.
8. The chimeric antigen receptor according to claim 1, wherein the linker domain consists of 117 to 121 amino acids.
9. The chimeric antigen receptor according to claim 1, wherein the linker domain consists of about 119 amino acids.
10. The chimeric antigen receptor according to any one of claims 1 to 9, wherein the linker domain comprises an amino acid sequence homologous to an immunoglobulin hinge region.
11. The chimeric antigen receptor according to any one of claims 1 to 9, wherein

the linker domain comprises an amino acid sequence homologous to an immunoglobulin hinge region of IgG, IgD, IgA, or the Constant Heavy (CH) 2 region of IgM or IgE, or a function variant thereof having at least 50%, 60%, 70%, 80%, 90%, 93%, 96% or 99% sequence identity.

12. The chimeric antigen receptor according to any one of claims 1 to 11, wherein the linker domain comprises an amino acid sequence homologous to a hinge region from an IgG isotype immunoglobulin, or a functional variant thereof having at least 50%, 60%, 70%, 80%, 90%, 93% or 96% sequence identity.

13. The chimeric antigen receptor according to any one of claims 1 to 11, wherein the linker domain comprises an amino acid sequence homologous to the hinge region of the IgG1, IgG2 or IgG4 subclass of immunoglobulin or a functional variant thereof having at least 50%, 60%, 70%, 80%, 90% or 93% sequence identity.

14. The chimeric antigen receptor according to any one of claims 1 to 13, wherein the linker domain comprises an amino acid sequence homologous to a hinge region from an IgG isotype immunoglobulin including a CXXC motif.

15. The chimeric antigen receptor according to claim 14, wherein the CXXC motif is selected from the group of CPPC, CPRC or CPSC

16. The chimeric antigen receptor according to any one of claims 1 to 15, wherein the linker domain comprises one or more amino acid sequences homologous to a constant heavy (CH) region of an immunoglobulin, or a functional variant thereof having at least 50%, 60%, 70%, 80%, 90%, 93% or 96% sequence identity.

17. The chimeric antigen receptor according to any one of claims 1 to 16, wherein the linker domain comprises an amino acid sequence homologous to one or more of a CH1 region, a CH2 region, a CH3 region and/or a CH4 region of an immunoglobulin, or a functional variant thereof having at least 50%, 60%, 70%, 80%, 90%, 93% or 96% sequence identity.

18. The chimeric antigen receptor according to any one of claims 1 to 16, wherein

the linker domain comprises an amino acid sequence homologous to one or more of a CH2 region and/or a CH3 region of an IgG isotype immunoglobulin, or a functional variant thereof having at least 50%, 60%, 70%, 80%, 90%, 95%, 98% or 99% sequence identity.

19. The chimeric antigen receptor according to any one of claims 1 to 18, wherein the linker domain consists of one or more immunoglobulin hinge region(s) and/or one or more CH region(s) of an immunoglobulin.

20. The chimeric antigen receptor according to any one of claims 1 to 19, wherein the linker domain consists of an IgG hinge region and one or more CH region(s) of an immunoglobulin.

21. The chimeric antigen receptor according to any one of claims 1 to 20, wherein the linker domain consists of an IgG hinge region and/or a CH2 or CH3 region of an immunoglobulin.

22. The chimeric antigen receptor according to any one of claims 1 to 21, wherein the linker domain comprises an amino acid sequence according to SEQ ID NOs: 9 to 17, or a functional variant having at least 50%, 60%, 70%, 80%, 90%, 93% or 96% sequence identity.

23. The chimeric antigen receptor according to any one of claims 1 to 21, wherein the linker domain comprises an amino acid sequence according to SEQ ID NOs: 9 to 13, or a functional variant thereof having at least 50%, 60%, 70%, 80%, 90%, 93% or 96% sequence identity.

24. The chimeric antigen receptor according to claims 1 to 23, wherein the chimeric antigen receptor does not comprise an amino acid sequence in the linker domain that substantially binds to an Fc receptor.

25. The chimeric antigen receptor according to any one of claims 1 to 24, wherein the chimeric antigen receptor when expressed in a CD8⁺ T cell has a cytotoxicity *in vitro* against target cells expressing a dysfunctional P2X7 receptor of at least 20%, at

a ratio of CAR expressing CD8+T cells : target cells of 30:1 or greater.

26. The chimeric antigen receptor according to any one of claims 1 to 25, wherein when expressed in a CD3+ T cell, the T cell demonstrates activity against as least 2 different cancer types, at least 3 different cancer types, at least 4 different cancer types, at least 5 different cancer types, at least 6 different cancer types, at least 7 different cancer types, at least 8 different cancer types, at least 9 different cancer types, at least 10 different cancer types.

27. The chimeric antigen receptor according to any one of claims 1 to 26, wherein the antigen-recognition domain recognises an epitope associated with an adenosine triphosphate (ATP)-binding site of the P2X7 receptor.

28. The chimeric antigen receptor according to any one of claims 1 to 27, wherein the dysfunctional P2X7 receptor has a reduced capacity to bind ATP compared to an ATP-binding capacity of a fully functional P2X7 receptor.

29. The chimeric antigen receptor according to any one of claims 1 to 28, wherein the dysfunctional P2X7 receptor has a conformational change that renders the receptor dysfunctional.

30. The chimeric antigen receptor according to claim 29, wherein the conformational change is a change of an amino acid from a trans-conformation to a cis-conformation.

31. The chimeric antigen receptor according to claim 30, wherein the amino acid that has changed from a trans-conformation to a cis-conformation is proline at amino acid position 210 of the dysfunctional P2X7 receptor.

32. The chimeric antigen receptor according to any one of claims 1 to 31, wherein the antigen-recognition domain recognises an epitope that includes one or more amino acid residues spanning from glycine at amino acid position 200 to cysteine at amino acid position 216 of the dysfunctional P2X7 receptor.

33. The chimeric antigen receptor according to any one of claim 1 to 32, wherein the antigen-recognition domain recognises an epitope that includes proline at amino acid position 210 of the dysfunctional P2X7 receptor.

34. The chimeric antigen receptor according to any one of claims 1 to 33, wherein the antigen-recognition domain comprises an amino acid sequence homologous to the amino acid sequence of an antigen binding domain of an antibody that binds to a dysfunctional P2X7 receptor, or wherein the antigen-recognition domain comprises the complementary determining regions of the heavy chain and/or light chain of an antibody that binds to a dysfunctional P2X7 receptor.

35. The chimeric antigen receptor according to any one of claims 1 to 34, wherein the transmembrane domain comprises all or part of the transmembrane domain of CD8 or CD28.

36. A nucleic acid molecule comprising a nucleotide sequence encoding the chimeric antigen receptor according to any one of claims 1 to 35.

37. A nucleic acid construct comprising a nucleic acid molecule according to claim 36.

38. A genetically modified cell, the cell comprising the chimeric antigen receptor according to any one of claims 1 to 35.

39. A genetically modified cell, the cell including the nucleic acid molecule according to claim 36 or the nucleic acid construct according to claim 37.

40. The genetically modified cell according to claims 38 or 39, wherein the cell is a leukocyte.

41. The genetically modified cell according to any one of claims 38 to 40, wherein the cell is a Peripheral Blood Mononuclear Cell (PBMC).

42. The genetically modified cell according to any one of claims 38 to 41, wherein

the cell is a lymphocyte.

43. The genetically modified cell according to any one of claims 38 to 42, wherein the cell is a T cell.

44. The genetically modified cell according to claim 43, wherein the T cell is a CD4+ T cell.

45. The genetically modified cell according to claim 43, wherein the T cell is a CD8+ T cell.

46. The genetically modified cell according to claim 43, wherein the T cell is a gamma delta T cell.

47. The genetically modified cell according to any one of claims 38 to 42, wherein the cell is a natural killer cell.

48. The genetically modified cell according to any one of claim 38 to 42, wherein the cell is a natural killer T cell.

49. The genetically modified cell according to any one of claim 38 to 42, wherein the cell is macrophage.

50. Use of a genetically modified cell according to any one of claims 38 to 49 or a cell expressing the chimeric antigen receptor according to any one of claims 1 to 35, for treating cancer.

51. Use according to claim 50, wherein the cancer is a solid cancer.

52. A method of killing a cell expressing a dysfunctional P2X7 receptor, the method comprising exposing the cell expressing a dysfunctional P2X7 receptor to a cell expressing a chimeric antigen receptor according to any one of claims 1 to 35, or the method comprises exposing the cell expressing a dysfunctional P2X7 receptor to a genetically modified cell according to any one of claims 38 to 49.

53. The method according to claim 52, wherein the cell expressing a dysfunctional P2X7 receptor is a cancer cell.

54. The method according to claim 53, wherein the cancer cell is a cell from a solid cancer.

55. The method according to claim 53 or claim 54, wherein the cancer cell is a breast cancer cell, a glioblastoma cancer cell, an ovarian cancer cell, or a melanoma cancer cell.

56. The method according to any one of claims 52 to 55, wherein the cell expressing the chimeric antigen receptor, or the genetically modified cell, is a cell autologous to the cell expressing a dysfunctional P2X7 receptor.

57. The method according to any one of claims 52 to 56, wherein the cell expressing a dysfunctional P2X7 receptor is within the body of a subject.

58. The method according to claim 57, wherein the cell within the body of a subject is a cell from a metastatic cancer.

59. A pharmaceutical composition comprising a genetically modified cell according to any one of claims 38 to 49, a nucleic acid molecule according to claims 36, or a nucleic acid construct according to claim 37, and a pharmaceutically acceptable carrier or excipient.

60. The use of a chimeric antigen receptor according to any one of claims 1 to 35 in the preparation of a medicament for the prevention or treatment of cancer.

61. A viral vector comprising a nucleic acid molecule according to claim 36 or nucleic acid construct according to claim 37.

62. The use of a viral vector according to claim 61 in the transduction of a cell for the prevention or treatment of cancer.

63. The Use of a nucleic acid molecule according to claim 36 or a nucleic acid construct according to claim 37 in the transduction, transformation or transfection of a cell.

64. A use according to claim 63, wherein the cell is used in the preparation of a medicament for the prevention or treatment of cancer.