

CLAIMS

1. A chimeric antigen receptor including an antigen-recognition domain and a signalling domain, wherein the antigen-recognition domain recognises a dysfunctional P2X₇ receptor.
2. The chimeric antigen receptor according to claim 1, wherein the antigen-recognition domain recognises an epitope associated with an adenosine triphosphate (ATP)-binding site of the dysfunctional P2X₇ receptor.
3. The chimeric antigen receptor according to claim 1 or claim 2, wherein the dysfunctional P2X₇ receptor has a reduced capacity to bind ATP compared to an ATP-binding capacity of a wild-type (functional) P2X₇ receptor.
4. The chimeric antigen receptor according to any one of claims 1 to 3, wherein the dysfunctional P2X₇ receptor has a conformational change that renders the receptor dysfunctional.
5. The chimeric antigen receptor according to claim 4, wherein the conformational change is a change of an amino acid from a trans-conformation to a cis-conformation.
6. The chimeric antigen receptor according to claim 5, 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.
7. The chimeric antigen receptor according to any one of claim 1 to 6, wherein the antigen-recognition domain recognises an epitope that includes proline at amino acid position 210 of the dysfunctional P2X₇ receptor.
8. The chimeric antigen receptor according to any one of claims 1 to 7, 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.
9. The chimeric antigen receptor according to any one of claims 1 to 8, wherein the antigen-recognition domain comprises amino acid sequence homology to the amino

- acid sequence of an antibody, or a fragment thereof, that binds to the dysfunctional P2X₇ receptor.
10. The chimeric antigen receptor according to any one of claims 1 to 9, wherein the antigen-recognition domain includes amino acid sequence homology to the amino acid sequence of a fragment-antigen binding (Fab) portion of an antibody that binds to a dysfunctional P2X₇ receptor.
 11. The chimeric antigen receptor according to any one of claim 9 or claim 10, wherein the antibody is a humanized antibody.
 12. The chimeric antigen receptor according to any one of claims 1 to 9, wherein the antigen-recognition domain includes amino acid sequence homology to the amino acid sequence of a single-chain variable fragment (scFv) that binds to a dysfunctional P2X₇ receptor.
 13. The chimeric antigen receptor according to any one of claims 1 to 9, wherein the antigen-recognition domain includes amino acid sequence homology to the amino acid sequence of a multivalent single-chain variable fragment (scFv) that binds to a dysfunctional P2X₇ receptor.
 14. The chimeric antigen receptor according to claim 13, wherein the multivalent single-chain variable fragment (scFv) is a di-valent or tri-valent scFv.
 15. The chimeric antigen receptor according to any one of claims 1 to 9, wherein the antigen-recognition domain includes amino acid sequence homology to the amino acid sequence of a single-antibody domain (sdAb) that binds to a dysfunctional P2X₇ receptor.
 16. The chimeric antigen receptor according to any one of claims 1 to 15, wherein the signalling domain includes a portion derived from an activation receptor.
 17. The chimeric antigen receptor according to claim 16, wherein the activation receptor is a member of the CD3 co-receptor complex.
 18. The chimeric antigen receptor according claim 17, wherein the portion derived from the CD3 co-receptor complex is CD3-ζ.

19. The chimeric antigen receptor according to claim 16, wherein the activation receptor is an Fc receptor.
20. The chimeric antigen receptor according claim 19, wherein the portion derived from the Fc receptor is FcεRI or FcγRI.
21. The chimeric antigen receptor according to any one of claims 1 to 15, wherein the signalling domain includes a portion derived from a co-stimulatory receptor.
22. The chimeric antigen receptor according to any one of claims 1 to 21, wherein the signalling domain includes a portion derived from an activation receptor and a portion derived from a co-stimulatory receptor.
23. The chimeric antigen receptor according to claim 21 or claim 22, wherein the co-stimulatory receptor is selected from the group consisting of CD27, CD28, CD30, CD40, DAP10, OX40, 4-1BB (CD137) and ICOS.
24. A nucleic acid molecule including a nucleotide sequence encoding the chimeric antigen receptor according to any one of claims 1 to 23.
25. A nucleic acid construct including a nucleic acid molecule according to claim 24.
26. The nucleic acid construct according to claim 25, wherein expression of the nucleic acid molecule is under the control of a transcriptional control sequence.
27. The nucleic acid construct according to claim 26, wherein the transcriptional control sequence is a constitutive promoter.
28. The nucleic acid construct according to claim 26, wherein the transcriptional control sequence is an inducible promoter.
29. The nucleic acid construct according to any one of claims 25 to 28, further including an Internal Ribosome Entry Site (IRES).
30. The nucleic acid construct according to any one of claims 25 to 29, wherein the nucleic acid construct is a vector.

31. The nucleic acid construct according to claim 30, wherein the vector is a viral vector.
32. A genetically modified cell, the cell including the chimeric antigen receptor of any one of claims 1 to 23.
33. The genetically modified cell according to claim 32, wherein the cell includes two or more different chimeric antigen receptors.
34. A genetically modified cell, the cell including the nucleic acid molecule according to claim 24, or the nucleic acid construct according to any one of claims 25 to 31, or a genomically integrated form of the nucleic acid construct.
35. The genetically modified cell according to claim 34, wherein the nucleic acid molecule or the nucleic acid construct encodes two or more different chimeric antigen receptors.
36. The genetically modified cell according to claim 33 or claim 35, wherein the two or more different chimeric antigen receptors have different signalling domains.
37. The genetically modified cell according to any one of claims 32 to 36, wherein the cell includes a first chimeric antigen receptor with a signalling domain including a portion derived from an activation receptor and a second chimeric antigen receptor with a signalling domain including a portion derived from a co-stimulatory receptor.
38. The genetically modified cell according to claim 37, wherein the activation receptor is a member of the CD3 co-receptor complex or is an Fc receptor.
39. The genetically modified cell according to claim 37 or claim 38, wherein the co-stimulatory receptor is selected from the group consisting of CD27, CD28, CD30, CD40, DAP10, OX40, 4-1BB (CD137) and ICOS.
40. The genetically modified cell according to any one of claims 32 to 36, wherein the cell is further modified so as to constitutively express co-stimulatory receptors.
41. The genetically modified cell according to claim 40, wherein the cell is further modified so as to express ligands for the co-stimulatory receptors, thereby facilitating auto-stimulation of the cell.

42. The genetically modified cell according to any one of claims 32 to 41, wherein the cell is further modified to secrete cytokines.
43. The genetically modified cell according to claim 42, wherein the cytokines are selected from the group consisting of IL-2, IL-7, IL-12, IL-15, IL-17 and IL-21, or a combination thereof.
44. The genetically modified cell according to any one of claims 32 to 43, wherein the cell is a leukocyte.
45. The genetically modified cell according to any one of claims 32 to 44, wherein the cell is a Peripheral Blood Mononuclear Cell (PBMC).
46. The genetically modified cell according to any one of claims 32 to 45, wherein the cell is a lymphocyte.
47. The genetically modified cell according to any one of claims 32 to 46, wherein the cell is a T cell.
48. The genetically modified cell according to claim 47, wherein the T cell is a CD4⁺ T cell.
49. The genetically modified cell according to claim 47, wherein the T cell is a CD8⁺ T cell.
50. The genetically modified cell according to any one of claims 32 to 46, wherein the cell is a natural killer cell.
51. The genetically modified cell according to any one of claim 32 to 46 wherein the cell is a natural killer T cell.
52. A method of killing a cell expressing a dysfunctional P2X₇ receptor, the method including exposing the cell expressing a dysfunctional P2X₇ receptor to a genetically modified cell having a chimeric antigen receptor, wherein the chimeric antigen receptor is directed against the dysfunctional P2X₇ receptor.

53. The method according to claim 52, wherein the chimeric antigen receptor directly recognises the dysfunctional P2X₇ receptor.
54. The method according to claim 52, wherein the chimeric antigen receptor recognises the dysfunctional P2X₇ receptor via an intermediate.
55. The method according to claim 54, wherein the intermediate is a probe that binds to a dysfunctional P2X₇ receptor and the chimeric antigen receptor recognises the probe.
56. The method of claim 52, further comprising the step of exposing the cell expressing a dysfunctional P2X₇ receptor to a probe.
57. The method according to claim 55 or claim 56, wherein the probe is an antibody or an aptamer.
58. The method according to any one of claims 55 to 57, wherein the probe includes a tag and the chimeric antigen receptor recognises the tag.
59. A method of killing a cell expressing a dysfunctional P2X₇ receptor, the method including exposing the cell expressing a dysfunctional P2X₇ receptor to a genetically modified cell according to any one of claims 32 to 51.
60. The method according to any one of claims 52 to 59, wherein the method further includes exposing the cell expressing a dysfunctional P2X₇ receptor to an exogenous cytokine.
61. The method according to any one of claims 52 to 60, wherein the genetically modified cell is a genetically modified cell autologous to the cell expressing a dysfunctional P2X₇ receptor.
62. The method according to any one of claims 52 to 61, wherein the cell expressing a dysfunctional P2X₇ receptor is within the body of a subject.
63. The method according to any one of claims 52 to 62, wherein the cell expressing a dysfunctional P2X₇ receptor is a cancer cell.

64. The method according to claim 63, wherein the cancer cell is selected from one or more of; brain cancer, oesophageal cancer, mouth cancer, tongue cancer, thyroid cancer, lung cancer, stomach cancer, pancreatic cancer, kidney cancer, colon cancer, rectal cancer, prostate cancer, bladder cancer, cervical cancer, epithelial cell cancers, skin cancer, leukaemia, lymphoma, myeloma, breast cancer, ovarian cancer, endometrial cancer and testicular cancer.
65. The method according to claim 63, wherein the cancer cell is selected from one or more of; lung cancer, oesophageal cancer, stomach cancer, colon cancer, prostate cancer, bladder cancer, cervical cancer, vaginal cancers, epithelial cell cancers, skin cancer, blood-related cancers, breast cancer, endometrial cancer, uterine cancer and testicular cancer.
66. The method according to any one of claims 63 to 65, wherein the cancer is metastatic.
67. The method according to any one of claims 63 to 66, wherein the cancer is stage III cancer.
68. The method according to any one of claims 63 to 66, wherein the cancer is stage IV cancer.
69. A method of expanding *in vitro* the genetically modified cell according to any one of claims 32 to 51, the method including the step of exposing the cell to an antigen for the chimeric antigen receptor.
70. The method according to claim 69, further including the step of exposing the cell to a cytokine.
71. A method of expanding *in vitro* the genetically modified cell according to any one of claims 32 to 51, the method including the step of exposing the cell to an antigen for the chimeric antigen receptor and simultaneously exposing the cell to a cytokine.
72. The method according to claim 70 or claim 71, wherein the cytokine is a member of the IL-2 subfamily, the interferon subfamily, the IL-10 subfamily, the IL-1 subfamily, the IL-17 subfamily or the TGF- β subfamily.

73. The method according to claim 70 or claim 71, wherein the cytokine is selected from the group consisting of IFN- γ , IL-2, IL-5, IL- 7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, IL-18, TNF- α , TGF- β 1, TGF- β 2, TGF- β 3 and GM-CSF, or a combination thereof.
74. A method of expanding *in vitro* the genetically modified cell according to any one of claims 32 to 51, the method including the step of exposing the cell to immobilised anti-CD3 and anti-CD28 antibodies.
75. A pharmaceutical composition including a genetically modified cell according to any one of claims 32 to 51 and a pharmaceutically acceptable carrier.
76. The pharmaceutical composition according to claim 75, further comprising a cytokine.
77. The pharmaceutical composition according to claim 76, wherein the cytokine is a member of the IL-2 subfamily, the interferon subfamily, the IL-10 subfamily, the IL-1 subfamily, the IL-17 subfamily or the TGF- β subfamily.
78. The pharmaceutical composition according to claim 76, wherein the cytokine is selected from the group consisting of IFN- γ , IL-2, IL-5, IL- 7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, IL-18, TNF- α , TGF- β 1, TGF- β 2, TGF- β 3 and GM-CSF, or a combination thereof.
79. The pharmaceutical composition according to any one of claims 75 to 78, further comprising an intermediate.
80. The pharmaceutical composition according to claim 79, wherein the intermediate is a probe that binds to a dysfunctional P2X₇ receptor and the chimeric antigen receptor recognises the probe.
81. The pharmaceutical composition according to claim 80, wherein the probe is an antibody or an aptamer.
82. The pharmaceutical composition according to claim 80 or claim 81, wherein the probe includes a tag and the chimeric antigen receptor recognises the tag.