CLAIMS

1. A chimeric antigen receptor (CAR) system comprising;

(i) a receptor component comprising an antigen binding domain, a transmembrane domain and a first binding domain; and

(ii) an intracellular signalling component comprising a signalling domain and a second binding domain which specifically binds the first binding domain of the receptor component;

in which the first binding domain or second binding domain is also capable of binding to an agent and in which binding of the first or second binding domain to the agent is of a higher affinity than binding of the first binding domain to the second binding domain, such that binding of the first and second binding domains is disrupted by the presence of the agent, such that in the absence of the agent the receptor component and the signalling component heterodimerize and binding of the antigen binding domain to antigen results in signalling through the signalling domain, whereas in the presence of the agent the receptor component and the signalling component do not heterodimerize and binding of the antigen binding domain to antigen does not result in signalling through the signalling domain.

2. A CAR system according to Claim 1 in which the receptor component comprises a linker between the transmembrane domain and the first binding domain.

3. A CAR system according to Claim 2 in which the linker comprises or consists of the sequence shown as SEQ ID NO: 3.

4. A CAR system according to any preceding claim in which the first binding domain comprises Tet Repressor Protein (TetR) and the second binding domain comprises Transcription inducing peptide (TiP); or in which the first binding domain comprises TiP and the second binding domain comprises TetR; and the agent is tetracycline, doxycycline or minocycline or an analogue thereof.

5. A CAR system according to Claim 4 in which the receptor component comprises two first binding domains which are TetR domains.

6. A CAR system according to Claim 5 in which the two TetR domains are separated by a linker.

7. A CAR system according to Claim 5 or 6 in which each TetR domain has a different affinity for the agent.

8. A CAR system according to any preceding claim, in which there are multiple receptor components, each recognizing a different antigen.

9. A CAR system according to Claim 8, in which the binding domain of the multiple receptor components differ in binding to the binding domain of the signalling component such that each antigen propagates different signalling strengths.

10. A CAR system according to Claim 8 or 9, in which the binding domains of the multiple receptor components differ in binding to the agent such that each antigen propagates different signalling strengths in the presence of the agent.

11. A CAR system according to any of Claims 1 to 9, in which the signalling domain of the signalling component comprises a single endodomain selected from CD3 zeta endodomain, CD28 endodomain, 41BB endodomain and OX40 endodomain.

12. A CAR system according to any preceding claim, in which the signalling domain of the signalling component comprises at least one of CD3 zeta endodomain, CD28 endodomain, 41BB endodomain and OX40 endodomain.

13. A CAR system according to any preceding claim which comprises a plurality of signalling components, each comprising a signalling domain and binding domain, in which the binding domains each recognise the same binding domain of the receptor component but the signalling domains comprise different endodomains.

14. A CAR system according to Claim 13 in which the plurality of signalling components comprise a plurality of binding domains, each of which independently recognise the binding domain of the receptor component with different affinities.

15. A nucleic acid sequence encoding a CAR signalling system according to any preceding claim, in which the receptor component and signalling component are co-expressed by means

of a self-cleaving peptide which is cleaved between the receptor component and the signalling component after translation.

16. A vector comprising a nucleic acid sequence according to Claim 15.

17. A vector according to Claim 16, which is a retroviral vector or a lentiviral vector or a transposon.

18. A T cell or NK cell which expresses a CAR system according to any of Claims 1 to 14.

19. A T cell or NK cell according to Claim 18 which comprises a nucleic acid according to Claim 15 or a vector according to Claim 16 or 17.

20. A pharmaceutical composition comprising a plurality of T cells or NK cells according to Claim 18 or 19.

21. A pharmaceutical composition according to Claim 20 for use in treating a disease.

22. A pharmaceutical composition for use according to Claim 21, in which the use comprises:

(i) isolation of a T cell or NK containing sample;

(ii) transduction or transfection of the T or NK cells with a nucleic acid sequence according to Claim 15 or a vector according to Claim 16 or 17; and

in which the T cells or NK cells from (ii) are to be administered to a subject.

23. A pharmaceutical composition for use according to Claim 21 or 22, in which the use involves monitoring toxic activity in the subject and in which an agent for use in the CAR signalling system according to any of Claims 1 to 14 is to be administered to the subject to reduce adverse toxic effects.

24. A pharmaceutical composition for use according to Claim 22 or 23, in which the use involves monitoring the progression of disease and/or monitoring toxic activity in the subject and in which an agent for use in the CAR signalling system according to any of Claims 1 to 14 is to be administered to the subject to provide acceptable levels of disease progression and/or toxic activity.

25. A pharmaceutical composition for use according to any of Claims 21 to 24, in which the disease is cancer.

26. Use of a pharmaceutical composition according to Claim 20 in the manufacture of a medicament for the treatment of cancer.

27. A kit which comprises a nucleic acid sequence according to Claim 15 or a vector according to Claim 16 or 17.

28. A method for making a T or NK cell according to Claim 18 or 19, which comprises the step of introducing a nucleic acid sequence according to Claim 15 or a vector according to Claim 16 or 17 into a T or NK cell *ex vivo*.

29. A method according to Claim 28 in which the T or NK cell is from a sample isolated from a subject.