

CLAIMS

1. An antibody comprising at least two different paratopes, each being specific for a different epitope of CD45.
2. An antibody according to claim 1, wherein the antibody is a biparatopic antibody wherein each of the two different paratopes of the antibody is specific for a different epitope of CD45.
3. An antibody according to claim 1 or 2, wherein:
(a) _____ the CD45 is a human CD45;:-
- ~~4. An antibody according to any one of the preceding claims, wherein (b) _____ the antibody is able to induce cell death of cells expressing CD45, preferably wherein the antibody does not induce the release of cytokines; and/or:-~~
- ~~5. An antibody according to any one of the preceding claims, wherein (c) _____ the antibody either lacks an Fc region or comprises an Fc region that has been silenced to remove one or more Fc effector functions and/or modified to alter serum pharmacokinetics.~~
- ~~46.~~ An antibody according to any one of ~~the preceding~~ claims 1 to 3, which is:
(a) _____ selected from a BYbe antibody, a TrYbe antibody, a diabody, a duobody, an IgG (for example an IgG with modifications to promote formation of heterodimers over homodimers and/or purification heterodimers, such as knob-in-hole modifications, charge-charge modifications and/or modification to alter the ability of one heavy chain to bind Protein A or an IgG4(P) antibody with FALA and knob-in-holes modifications); or:-
- ~~7. An antibody according to any one of the preceding claims, wherein the antibody is~~
(b) _____ a humanized antibody or a fully human antibody.

8. ~~A nucleic acid molecule or molecules encoding an antibody as defined in any one of the preceding claims.~~
9. ~~A vector or vectors encoding an antibody as defined in any one of claims 1 to 7 or comprising a nucleic acid molecule or molecules according to claim 8.~~
10. ~~A pharmaceutical composition comprising:
(a) ~~an antibody according to any one of claims 1 to 7, a nucleic acid molecule or molecules according to claim 8, or a vector or vectors according to claim 9; and~~
(b) ~~a pharmaceutically acceptable carrier or diluent.~~~~
11. ~~A pharmaceutical composition according to claim 10 for use in a method of therapy.~~
12. ~~A pharmaceutical composition of claim 11 for use in a method of killing disease-associated, CD45-expressing cells in a subject.~~
13. ~~A pharmaceutical composition of claim 11 or 12 for use in a method of treating a blood cancer, for example leukemia, lymphoma or multiple myeloma.~~
14. ~~A pharmaceutical composition of claim 11 or 12 for use in a method of treating an autoimmune disease, for example multiple sclerosis or scleroderma.~~
15. ~~A pharmaceutical composition for use in the method of any one of claims 11 to 14, wherein the method further comprises transferring cells to the subject after the cell depletion.~~
16. ~~A method of depleting disease-causing, CD45-expressing cells in a subject, the method comprising administering a pharmaceutical composition according to claim 10 to the subject.~~

- ~~17.— A method of claim 16 for treating a blood cancer, for example leukemia, lymphoma or multiple myeloma.~~
- ~~18.— A method of claim 16 for treating an autoimmune disease, for example multiple sclerosis or scleroderma.~~
- ~~19.— A method of any one of claim 16, 17, and 18, wherein the method further comprises transferring cells to the subject after the cell depletion.~~
- ~~20.— Use of an antibody according to any one of claims 1 to 7, a nucleic acid molecule or molecules according to claim 8 or a vector or vector according to claim 9 in the manufacture of a medicament for killing disease-associated, CD45-expressing cells in a subject.~~
- ~~21.— The use of claim 20 wherein the medicament is for treating a blood cancer, for example leukemia, lymphoma or multiple myeloma.~~
- ~~22.— The use of claim 20 wherein the medicament is for treating an autoimmune disease, for example multiple sclerosis or scleroderma.~~
- ~~23.— The use of any one of claims 20 to 22, wherein the medicament is for use in a method that further comprises transferring cells to the subject after the cell killing.~~
524. A binding molecule or molecules that are able to multimerise CD45 to induce cell death of a cell expressing CD45 without also inducing significant cytokine release.
625. The binding molecule or molecules according to claim 524, wherein the binding molecule or molecules are an antibody that specifically binds CD45 or a mixture of at least two different antibodies that specifically bind CD45.

726. The binding molecule or molecules according to claim 625, wherein the antibody or the antibodies of the mixture have an Fc region which is/are modified:

- (a) to be an effector optimized Fc region;
- (b) to increase formation of heterodimers over homodimers (such as have knob-in-hole modifications);
- (c) to have charged residues present that promote the formation of heterodimers over homodimers;
- (d) to have altered serum pharmacokinetics and/or
- (e) to have altered protein A binding.

827. The binding molecule or molecules according to claim ~~25 or 266~~, wherein the antibody or the antibodies in the mixture of antibodies:

- (a) have silenced Fc regions.

~~28. The binding molecule or molecules according to claim 25, wherein the antibody or the antibodies of the mixture of antibodies lack Fc regions; or:~~

~~29. The binding molecule or molecules according to claim 25, wherein the antibody or antibodies of the mixture (b)~~ are selected from a BYbe antibody, a TrYbe antibody, a diabody, a duobody, an IgG, or a knob-in-hole modified IgG, in particular where the antibody or antibodies are IgG4(P) FALA knob-in-hole format.

930. The binding molecule or molecules according to any one of claims ~~24 to 295 to 8~~, wherein:

- (a) the binding molecule is an antibody comprising at least two antigen-binding sites having different specificities for CD45; or
- (b) the binding molecules are a mixture of antibodies, where collectively the antibodies in the mixture comprise at least two different antigen-binding sites having different specificities for CD45.

1031. The binding molecule or molecules according to claim 930, which is a mixture of antibodies, where each antibody has a single specificity for CD45, but the mixture comprises at least two different antibodies having a different specificity for CD45.

1132. The binding molecule or molecules according to any one of claims 5 to 1024 to 31, wherein:

(a) the antibody or antibodies are chimaeric, humanized or fully human antibodies;
or:

~~33. The binding molecule or molecules according to any one claims 24 to 32, wherein (b)~~
the antibody or antibodies of the mixture comprise an antigen-binding site specific for serum albumin.

1234. A nucleic acid molecule or molecules encoding an antibody according to any one of claims 1 to 4 or a binding molecule or molecules ~~as defined in~~ according to any one of claims 5 to 1124 to 33.

1335. A vector or vectors encoding an antibody according to any one of claims 1 to 4 or a binding molecule or molecules as defined in any one of claims 5 to 1124 to 33 or comprising a nucleic acid molecule or molecules according to claim 1234, for instance where the vector is a LNP-mRNA.

1436. A pharmaceutical composition comprising:

- (a) an antibody according to any one of claims 1 to 4, a binding molecule or molecules according to any one of claims 5 to 1124 to 33, a nucleic acid molecule or molecules according to claim 1234, or a vector or vectors according to claim 1335; and
- (b) a pharmaceutically acceptable carrier or diluent.

1537. An antibody according to any one of claims 1 to 4, a binding molecule or binding molecules according to any one of claims 5 to 11, a nucleic acid molecule or molecules

according to claim 12, a vector or vectors according to claim 13, or a pharmaceutical composition according to claim 14~~36~~ for use in a method of therapy.

~~38.— A pharmaceutical composition according to claim 37 for use in a method of killing disease-associated CD45-expressing cells in a subject.~~

~~39.— A pharmaceutical composition according to claim 37 or 38 for use in a method of treating a blood cancer, for example leukemia, lymphoma or multiple myeloma.~~

~~40.— A pharmaceutical composition according to claim 37 or 38 for use in a method of treating an autoimmune disease, for example multiple sclerosis or scleroderma.~~

~~41.— A pharmaceutical composition according to any one of claims 37 or 38, wherein the method further comprises transferring cells to the subject after the cell killing.~~

~~42.— A method of killing disease-associated, CD45-expressing cells in a subject, the method comprising administering a pharmaceutical composition according to claim 36 to the subject.~~

~~43.— The method of claim 42 for treating a blood cancer, for example leukemia, lymphoma or multiple myeloma.~~

~~44.— The method of claim 42 for treating an autoimmune disease, for example multiple sclerosis or scleroderma.~~

~~45.— The method of any one of claims 42 to 44, wherein the method further comprises transferring cells to the subject after the cell killing.~~

1646. Use of an antibody according to any one of claims 1 to 4, a binding molecule or molecules according to any one of claims 5 to 11~~24 to 33~~, a nucleic acid molecule or molecules

according to claim ~~1234~~, or a vector or vectors according to claim ~~1335~~ in the manufacture of a medicament for killing disease-associated, CD45-expressing cells in a subject.

~~1747~~. The use of claim ~~1646~~ wherein the medicament is for:

(a) ~~_____~~ treating a blood cancer, for example leukemia, lymphoma or multiple myeloma;

~~48.~~ ~~The use of claim 46 wherein the medicament is for (b) _____~~ treating an autoimmune disease, for example multiple sclerosis or scleroderma.

~~49.~~ ~~The use of any one of claims 46 to 48, wherein the medicament is for (c) _____~~ use in a method that further comprises transferring cells to the subject after the cell killing.

~~1850~~. A method of screening for a binding molecule or molecules able to multimerise CD45 to induce cell death, the method comprising:

- (a) contacting a binding molecule or molecules that are able to bind CD45 with target cells expressing CD45; and
- (b) determining whether the target cells undergo cell death.

~~1951~~. The method of claim ~~1850~~, wherein the method further comprises:

- (c) determining whether cytokines are released in the test sample, for example where the level of one or more of CCL2, GM-CSF, IL-1RA, IL-6, IL-8, IL-10, IL-11, and M-CSF is measured.

~~2052~~. The method of claim ~~18 or 1950 or 51~~, wherein:

- (i) the binding molecule or molecules have already been identified as able to multimerise CD45; or
- (ii) the method comprises first screening binding molecules specific for CD45 for their ability to multimerise CD45, for example by screening permutations of two or more different binding molecules for their ability to multimerise CD45.

2153. An *ex vivo* method of depleting or killing target cells expressing CD45 in a population of cells, tissue, or organ comprising contacting said cells tissue or organ with an antibody according to any one of claims 1 to 47 or a binding molecule according to any one of claims 5 to 1124 to 33.

~~54. An antibody according to any one of claims 1 to 7 or a binding molecule according to any one of claims 24 to 33 for use in a method of treating or preventing graft versus host disease (GVHD) in a subject, the method comprising~~

~~— (a) — contacting *ex vivo* a population of cells, tissue, or organ with an antibody according to any one of claims 1 to 7 or a binding molecule according to any one of claims 24 to 33 to kill target cells expressing CD45; and~~

~~— (b) — transplanting the treated population of cells, tissue, or organ to said subject.~~

~~55. A method of treating or preventing graft versus host disease (GVHD) comprising:~~

~~— (a) — contacting a population of cells, tissue, or organ with an antibody e according to any one of claims 1 to 7 or a binding molecule according to any one of claims 24 to 33 to kill target cells expressing CD45 *ex vivo*; and~~

~~— (b) — transplanting the treated population of cells, tissue, or organ to a subject in need of such a transplantation.~~

2256. Use of an antibody according to any one of claims 1 to 47 or a binding molecule according to any one of claims 5 to 1124 to 33 for use in the manufacture of a medicament for treating or preventing graft versus host disease (GVHD) in a method comprising:

(a) contacting a population of cells, tissue, or organ with an antibody according to any one of claims 1 to 47 or a binding molecule according to any one of claims 5 to 1124 to 33 to kill target cells expressing CD45 *ex vivo*; and

(b) transplanting the treated population of cells, tissue, or organ to a subject in need of such a transplantation.