CLAIMS

1. An antibody or functional fragment thereof comprising at least one variable binding domain consisting of a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein said binding domain comprises two paratopes for two unrelated epitopes, wherein (i) binding of each paratope to its epitope does not prevent the simultaneous binding of the other paratope to its respective epitope, and wherein (ii) both paratopes comprise at least one residue from at least one VH CDR and at least one residue from at least one VL CDR.

2. The antibody or functional fragment thereof of claim 1, which is a bispecific antibody, wherein said two unrelated epitopes are present on two different molecules.

3. The antibody or functional fragment thereof of claim 1 or 2, wherein the amount of binding of each paratope to its respective epitope in the simultaneous presence of both epitopes is at least 25% of the amount of binding that is achieved in the absence of the other epitope under otherwise identical conditions.

4. The antibody or functional fragment thereof of claim 3, wherein the amount of binding is at least 50%, particularly at least 75%, and more particularly at least 90%.

5. The antibody or functional fragment thereof of any one of claim 1 to 4, wherein the first paratope comprises residues from CDR1 and CDR3 of the VL domain and CDR2 of the VH domain, and the second paratope comprises residues from CDR1 and CDR3 of the VH domain and CDR2 of the VL domain.

6. The antibody or functional fragment thereof of any one of claims 1 to 5 that is a human antibody or functional fragment thereof.

7. The antibody or functional fragment thereof of claim 6 that is based on a human VH3 family heavy chain sequence and a human Vkappa1 family light chain sequence.

8. The antibody or functional fragment thereof of claim 6 that is based on a human VH3 family heavy chain sequence and a human Vlambda1 family light chain.

9. The antibody or functional fragment thereof of any one of claims 1 to 8, wherein the antibody or functional fragment thereof is selected from a single chain Fv fragment, a Fab fragment and an IgG.

10. A nucleic acid sequence encoding the antibody or functional fragment thereof according to any one of claims 1 to 9.

11. A vector comprising the nucleic acid sequence according to claim 10.

12. A host cell comprising the nucleic acid sequence according to claim 10, or the vector according to claim 11.

13. A method for generating the antibody or functional fragment thereof of any one of claims 1 to 9, comprising the step of expressing the nucleic acid sequence according to claim 10, or the vector according to claim 11, either *in vitro* or from an appropriate host cell, including the host cell according to claim 12.

14. A collection of antibodies or functional fragment thereof, wherein said collection comprises a diverse collection of antibody variable domain sequences wherein either (i) at least 3 CDR residues from Lib1 positions are diversified, provided that at least one diversified residue is located within the VH domain and at least one diversified position is located within the VL domain, and wherein no residues from Lib2 positions are diversified, or (ii) at least 3 CDR residues from Lib2 positions are diversified, provided that at least one diversified residue is located within the VH domain and at least one diversified position is located within the VL domain, and wherein no residues from Lib1 positions are diversified;

    wherein

    (i) the Lib1 positions are VL24, VL25, VL26, VL27, VL28 (provided that the CDR-L1 length is 11; if the length is 10, then the residue number is 29; if the length is 12 or more, then the residue number is 27a), VL29 (provided that CDR-L1 length is 11; if the length is 10, then the residue number is 30; if the length is 12, then the residue number is 28; if the length is 13 or more, then the residue number is 27b), VL93, VL94, VL95 (only in case of libraries comprising Vlambda light chains), VL95a (only in case of libraries comprising Vlambda light chains), VL95b (only in case of libraries comprising Vlambda light chains), VH58, VH59, VH60, VH61, VH62, VH63, VH64, and VH65;

    (ii) the Lib2 positions are VH26, VH27, VH28, VH29, VH30, VH31, VH32, VH94, VH96-VH99, VH102, VL49, VL53, VL54, VL55, and VL56.

15. The collection of antibodies or functional fragment thereof of claim 14, wherein in the case of (i) at least one residue of each of CDR1 and CDR3 of the VL domain and CDR2 of the VH is diversified, or in the case of (ii) at least one residue of each of CDR1 and CDR3 of the VH domain and CDR2 of the VL is diversified.

16. The collection of antibodies or functional fragment thereof of claim 14, wherein in the case of (i) at least one residue of the Lib1E positions in said variable binding domain is additionally diversified, and/or wherein in the case of (ii) at least one residue of the Lib2E positions in said variable binding domain is additionally diversified;

wherein

(i) the Lib1E positions are VL1, VL2, VL3, VL69, VL70, VL100, and VH46;

(ii) the Lib2E positions are VH1, VH2, VH3, VH25, VH76, VH105, VL45, VL57, and VL58.

17. A method of generating a bispecific antibody molecule or functional fragment thereof comprising the steps of

a. generating a first collection of antibody molecules or functional fragments thereof, each comprising a heterodimeric VH-VL variable region, with diversity in at least 3 CDR positions selected from the group of Lib1, provided that at least one diversified residue is located within the VH domain and at least one diversified position is located within the VL domain, and wherein no residues from Lib2 positions are diversified;

b. selecting a first antibody molecule or functional fragment thereof specific for a first target or epitope from said first collection;

c. generating a second collection of antibody molecules or functional fragments thereof, each comprising a heterodimeric VH-VL variable region, with diversity in at least 3 CDR positions selected from the group of Lib2, provided that at least one diversified residue is located within the VH domain and at least one diversified position is located within the VL domain, and wherein no residues from Lib1 positions are diversified;

d. selecting a second antibody molecule or functional fragment thereof specific for a second target or epitope from said second collection; and

e. generating a nucleic acid sequence that encodes a third antibody molecule or functional fragment thereof comprising a heterodimeric VH-VL variable region, wherein the third antibody molecule or functional fragment thereof comprises at least 3 residues found in the group of Lib1 positions in the first antibody molecule or functional fragment thereof, of which at least one residue is located within the VH domain and at least one residue is located within the VL domain, and wherein the third antibody molecule or functional fragment thereof further comprises at least 3 residues found in the group of Lib2 positions in the second antibody molecule or functional fragment thereof, of which at least one residue is located within the VH domain and at least one residue is located within the VL domain;

wherein

(i) the Lib1 positions are VL24, VL25, VL26, VL27, VL28 (provided that the CDR-L1 length is 11; if the length is 10, then the residue number is 29; if the length is 12 or more, then the residue number is 27a), VL29 (provided that CDR-L1 length is 11; if the length is 10, then the residue number is 30; if the length is 12, then the residue number is 28; if the length is 13 or more, then the residue number is 27b), VL93, VL94, VL95 (only in case of libraries comprising Vlambda light chains), VL95a (only in case of libraries comprising Vlambda light chains), VL95b (only in case of libraries comprising Vlambda light chains), VH58, VH59, VH60, VH61, VH62, VH63, VH64, and VH65; and
(ii) the Lib2 positions are VH26, VH27, VH28, VH29, VH30, VH31, VH32, VH94, VH96-VH99, VH102, VL49, VL53, VL54, VL55, and VL56.

18. A method of generating a bispecific antibody molecule or functional fragment thereof comprising the steps of

a. generating a first collection of antibody molecules or functional fragments thereof, each comprising a heterodimeric VH-VL variable region, with diversity in at least 3 CDR positions selected from the group of Lib1, provided that at least one diversified residue is located within the VH domain and at least one diversified position is located within the VL domain, and wherein no residues from Lib2 positions are diversified;

b. selecting a first antibody molecule or functional fragment thereof specific for a first target or epitope from said first collection;

c. generating a second collection of antibody molecules or functional fragments thereof, each comprising a heterodimeric VH-VL variable region, by diversifying said first antibody molecule of functional fragment thereof by introducing diversity in at least 3 CDR positions selected from the group of Lib2, provided that at least one diversified residue is located within the VH domain and at least one diversified position is located within the VL domain, and wherein no residues from Lib1 positions are diversified; and

d. selecting a second antibody molecule or functional fragment thereof specific for said first and a second target or epitope from said second collection; and

e. alternatively, performing steps a. to d. with the modification that the first collection in step a. is generated by diversifying at least 3 CDR positions selected from the group of Lib2, and diversifying in step c. said first antibody or antibody fragment thereof in at least 3 CDR positions selected from the group of Lib1;

wherein

(i) the Lib1 positions are VL24, VL25, VL26, VL27, VL28 (provided that the CDR-L1 length is 11; if the length is 10, then the residue number is 29; if the length is 12 or more, then the residue number is 27a), VL29 (provided that CDR-L1 length is 11; if the length is 10, then the residue number is 30; if the length is 12, then the residue number is 28; if the length is 13 or more, then the residue number is 27b), VL93, VL94, VL95 (only in case of libraries comprising Vlambda light chains), VL95a (only in case of libraries comprising Vlambda light chains), VL95b (only in case of libraries comprising Vlambda light chains), VH58, VH59, VH60, VH61, VH62, VH63, VH64, and VH65; and
(ii) the Lib2 positions are VH26, VH27, VH28, VH29, VH30, VH31, VH32, VH94, VH96-VH99, VH102, VL49, VL53, VL54, VL55, and VL56.

19. The method of claim 17 or 18, further comprising the step of.

f. expressing the nucleic acid sequence generated in steps a. to e. in a host cell or translating the nucleic acid into protein representing the third antibody molecule or functional fragment thereof.

20. The method of any one of claims 17 to 19, wherein any of said collection having diversity selected from group Lib1 includes additional diversity in at least one enhancing position selected from the group of Lib1E and/or wherein any of said collection having diversity selected from group Lib1 includes additional diversity in at least one enhancing position selected from the group of Lib2E;

wherein

(i) the Lib1E positions are VL1, VL2, VL3, VL69, VL70, VL100, and VH46;
(ii) the Lib2E positions are VH1, VH2, VH3, VH25, VH76, VH105, VL45, VL57, and VL58.

21. The method according to any one of claims 17 to 20, wherein said first collection is identical to a library selected from Lib D1L1, Lib D1L2 and Lib D2L1, or is derived from such a library having the diversified positions present in Lib D1L1, Lib D1L2 or Lib D2L1 in combination with more than 90% sequence identity, particularly more than 95%

sequence identity, in the framework regions; and wherein said first collection is identical to a library selected from Lib D1H1, Lib D1H2, Lib D1H3 and Lib D2H1, or is derived from such a library having the diversified positions present in Lib D1H1, Lib D1H2, Lib D1H3 or Lib D2H1 in combination with more than 90% sequence identity, particularly more than 95% sequence identity, in the framework regions;

wherein the libraries Lib D1L1, Lib D1L2, Lib D2L1, Lib D1H1, Lib D1H2, Lib D1H3 and Lib D2H1 are shown in Figure 4.

22. The method of any one of claims 17 to 21, wherein the antibody molecule or functional fragment thereof is selected from a single chain Fv fragment, a Fab fragment and an IgG.

CLAIMS

1. An antibody or functional fragment thereof comprising at least one variable binding domain consisting of a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein said binding domain comprises two paratopes for two unrelated epitopes, wherein (i) binding of each paratope to its epitope does not prevent the simultaneous binding of the other paratope to its respective epitope, and wherein (ii) both paratopes comprise at least one residue from at least one VH CDR and at least one residue from at least one VL CDR.

2. The antibody or functional fragment thereof of claim 1, which is a bispecific antibody.

3. The antibody or functional fragment thereof of claim 1 or 2, wherein the amount of binding of each paratope to its respective epitope in the simultaneous presence of both epitopes is at least 25% of the amount of binding that is achieved in the absence of the other epitope under otherwise identical conditions.

4. The antibody or functional fragment thereof of claim 3, wherein the amount of binding is at least 50%, particularly at least 75%, and more particularly at least 90%.

5. The antibody or functional fragment thereof of any one of claim 1 to 4, wherein the first paratope comprises residues from CDR1 and CDR3 of the VL domain and CDR2 of the VH domain, and the second paratope comprises residues from CDR1 and CDR3 of the VH domain and CDR2 of the VL domain.

6. The antibody or functional fragment thereof of any one of claims 1 to 5 that is a human antibody or functional fragment thereof.

7. The antibody or functional fragment thereof of claim 6 that is based on a human VH3 family heavy chain sequence and a human Vkappa1 family light chain sequence.

8. The antibody or functional fragment thereof of claim 6 that is based on a human VH3 family heavy chain sequence and a human Vlambda1 family light chain.

9. The antibody or functional fragment thereof of any one of claims 1 to 8, wherein the antibody or functional fragment thereof is selected from a single chain Fv fragment, a Fab fragment and an IgG.

10. A nucleic acid sequence encoding the antibody or functional fragment thereof according to any one of claims 1 to 9.

11. A vector comprising the nucleic acid sequence according to claim 10.

12. A host cell comprising the nucleic acid sequence according to claim 10, or the vector according to claim 11.

13. A method for generating the antibody or functional fragment thereof of any one of claims 1 to 9, comprising the step of expressing the nucleic acid sequence according to claim 10, or the vector according to claim 11, either *in vitro* or from an appropriate host cell, including the host cell according to claim 12.

14. A collection of antibodies or functional fragment thereof, wherein said collection comprises a diverse collection of antibody variable domain sequences wherein either (i) at least 3 CDR residues from Lib1 positions are diversified, provided that at least one diversified residue is located within the VH domain and at least one diversified position is located within the VL domain, and wherein no residues from Lib2 positions are diversified, or (ii) at least 3 CDR residues from Lib2 positions are diversified, provided that at least one diversified residue is located within the VH domain and at least one diversified position is located within the VL domain, and wherein no residues from Lib1 positions are diversified.

15. The collection of antibodies or functional fragment thereof of claim 14, wherein in the case of (i) at least one residue of each of CDR1 and CDR3 of the VL domain and CDR2 of the VH is diversified, or in the case of (ii) at least one residue of each of CDR1 and CDR3 of the VH domain and CDR2 of the VL is diversified.

16. The collection of antibodies or functional fragment thereof of claim 14, wherein in the case of (i) at least one residue of the Lib1E positions in said variable binding domain is additionally diversified, and/or wherein in the case of (ii) at least one residue of the Lib2E positions in said variable binding domain is additionally diversified.

17. A method of generating a bispecific antibody molecule or functional fragment thereof comprising the steps of

a. generating a first collection of antibody molecules or functional fragments thereof, each comprising a heterodimeric VH-VL variable region, with diversity in at least 3 CDR positions selected from the group of Lib1, provided that at least one diversified residue is located within the VH domain and at least one diversified position is located within the VL domain, and wherein no residues from Lib2 positions are diversified;

b. selecting a first antibody molecule or functional fragment thereof specific for a first target or epitope from said first collection;

c. generating a second collection of antibody molecules or functional fragments thereof, each comprising a heterodimeric VH-VL variable region, with diversity in at least 3 CDR positions selected from the group of Lib2, provided that at least one diversified residue is located within the VH domain and at least one diversified position is located within the VL domain, and wherein no residues from Lib1 positions are diversified;

d. selecting a second antibody molecule or functional fragment thereof specific for a second target or epitope from said second collection; and

e. generating a nucleic acid sequence that encodes a third antibody molecule or functional fragment thereof comprising a heterodimeric VH-VL variable region, wherein the third antibody molecule or functional fragment thereof comprises at least 3 residues found in the group of Lib1 positions in the first antibody molecule or functional fragment thereof, of which at least one residue is located within the VH domain and at least one residue is located within the VL domain, and wherein the third antibody molecule or functional fragment thereof further comprises at least 3 residues found in the group of Lib2 positions in the second antibody molecule or functional fragment thereof, of which at least one residue is located within the VH domain and at least one residue is located within the VL domain.

18. A method of generating a bispecific antibody molecule or functional fragment thereof comprising the steps of

a. generating a first collection of antibody molecules or functional fragments thereof, each comprising a heterodimeric VH-VL variable region, with diversity in at least 3 CDR positions selected from the group of Lib1, provided that at least one diversified residue is located within the VH domain and at least one diversified position is located within the VL domain, and wherein no residues from Lib2 positions are diversified;

b. selecting a first antibody molecule or functional fragment thereof specific for a first target or epitope from said first collection;

c. generating a second collection of antibody molecules or functional fragments thereof, each comprising a heterodimeric VH-VL variable region, by diversifying said first antibody molecule of functional fragment thereof by introducing diversity in at least 3 CDR positions selected from the group of Lib2, provided that at least one diversified residue is located within the VH domain and at least one diversified position is located within the VL domain, and wherein no residues from Lib1 positions are diversified; and

d. selecting a second antibody molecule or functional fragment thereof specific for said first and a second target or epitope from said second collection, and

e. alternatively, performing steps a. to d. with the modification that the first collection in step a. is generated by diversifying at least 3 CDR positions selected from the group of Lib2, and diversifying in step c. said first antibody or antibody fragment thereof in at least 3 CDR positions selected from the group of Lib1.

19. The method of claim 17 or 18, further comprising the step of.

f. expressing the nucleic acid sequence generated in steps a. to e. in a host cell or translating the nucleic acid into protein representing the third antibody molecule or functional fragment thereof.

20. The method of any one of claims 17 to 19, wherein any of said collection having diversity selected from group Lib1 includes additional diversity in at least one enhancing position selected from the group of Lib1E and/or wherein any of said collection having diversity selected from group Lib1 includes additional diversity in at least one enhancing position selected from the group of Lib2E.

21. The method according to any one of claims 17 to 20, wherein said first collection is identical to a library selected from Lib D1L1, Lib D1L2 and Lib D2L1, or is derived from such a library having the diversified positions present in Lib D1L1, Lib D1L2 or Lib D2L1 in combination with more than 90% sequence identity, particularly more than 95% sequence identity, in the framework regions; and wherein said first collection is identical to a library selected from Lib D1H1, Lib D1H2, Lib D1H3 and Lib D2H1, or is derived from such a library having the diversified positions present in Lib D1H1, Lib D1H2, Lib D1H3 or Lib D2H1 in combination with more than 90% sequence identity, particularly more than 95% sequence identity, in the framework regions.

22. The method of any one of claims 17 to 21, wherein the antibody molecule or functional fragment thereof is selected from a single chain Fv fragment, a Fab fragment and an IgG.