[0026] Thus, there is still a large unmet need to provide an improved format for the bispecific antibodies that incorporates the advantages of having two paratopes within one complementary heterodimeric VH-VL pair, while avoiding the problems observed with the prior art constructs.

[0027] The solution for this problem that has been provided by the present invention, i.e. the design of two paratopes for each complementary heterodimeric VH-VL pair, wherein each paratope uses residues from CDR regions from both VH and VL domains, has so far not been achieved or suggested by the prior art.

SUMMARY OF THE DISCLOSURE~~INVENTION~~

[0028] The present ~~invention~~disclosure relates to bispecific antibodies characterized by having two paratopes for each complementary heterodimeric VH-VL pair, wherein each paratope uses residues from CDR regions from both VH and VL domains.

[0029] Thus, in a first aspect, the present ~~invention~~disclosure relates to 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.

[0029a] In another aspect, there is provided 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, 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.

[0030] In a second aspect, the present ~~invention~~disclosure relates to nucleic acid sequence encoding the antibody or functional fragment thereof according to the present ~~invention~~disclosure.

[0031] In a third aspect, the present ~~invention~~disclosure relates to a vector comprising the nucleic acid sequence according to the present ~~invention~~disclosure.

[0032] In a fourth aspect, the present ~~invention~~disclosure relates to a host cell comprising the nucleic acid sequence according to the present ~~invention~~disclosure, or the vector according to the present ~~invention~~disclosure.

[0033] In a fifth aspect, the present ~~invention~~disclosure relates to a method for generating the antibody or functional fragment thereof according to the present ~~invention~~disclosure, comprising the step of expressing the nucleic acid sequence according to the present ~~invention~~disclosure, or the vector according to the present ~~invention~~disclosure, either *in vitro* or from an appropriate host cell, including the host cell according to the present ~~invention~~disclosure.

[0034] In a sixth aspect, the present ~~invention~~disclosure relates to 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.

[0034a] In another aspect, there is provided 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.

[0035] In a seventh aspect, the present ~~invention~~disclosure relates to 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 fragment 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

[0035a] In another aspect, there is provided 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.

[0036] In an eighth aspect, the present disclosure~~invention~~ relates to 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 fragment 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 fragment 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.

[0036a] In another aspect, there is provided 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.

[0037] In a ninth aspect, the present disclosure~~invention~~ relates to pharmaceutical compositions comprising an antibody molecule or functional fragment thereof, and optionally a pharmaceutically acceptable carrier and/or excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] **Figure 1** below shows the list of preferred CDR positions of which all or a subset should be diversified in antibody libraries in some embodiments of our present invention (A), the list of preferred optional enhancing positions in the framework regions which may also be diversified in antibody libraries in some embodiments of the invention (B), and the list of CDR positions of which all or a subset are preferably left invariant in all libraries of the present invention, i.e. both in libraries in which Lib1 residues are diversified and in libraries in which Lib2 residues are diversified (C).

[0039] **Figure 2** below illustrates in a schematic way the discovery process of the novel bi-specific antibodies, using the top view (aerial) perspective to show how a heterodimeric VH-VL antibody scaffold is first diversified separately in two regions representing Lib1 and Lib2 CDR residues; this yields two libraries that are separately selected to obtain two antibody clones, with one clone binding a first target or epitope via a first paratope and the second clone binding a second target or epitope via a second paratope; these clones are then combined into a bi-specific antibody according to the present invention, by introducing target-specific residues selected in Lib1 positions in the first antibody clone into the second antibody clone, or by introducing target-specific residues selected in Lib2 positions in the second antibody clone into the first antibody clone. Figure 2 also illustrates in a schematic way the location of those potential enhancing residues according to the current invention in the framework regions that are visible from the top view (aerial) perspective.

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Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Xaa Xaa Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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35 40 45

Tyr Ala Ala Ser Ser Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
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Ser Gly Ser Gly Xaa Xaa Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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Leu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
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Thr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Gly Asn Asn Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95

Asn Gly Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 13
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<223> Xaa: diversified position

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<222> (1)..(2)
<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

<400> 13

Xaa Xaa Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Xaa Xaa Xaa Asn Ile Gly Xaa Asn
20 25 30

Thr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Gly Asn Asn Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Xaa Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Xaa Xaa Xaa
85 90 95

Xaa Gly Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 14
<211> 117
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<220>
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<400> 14

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Asn
            20                  25                  30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Thr Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Asn Asp Asn Val
    50                  55                  60

Leu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Thr Ser Ser Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210>  15
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<220>
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<222>  (59)..(59)
<223>  Xaa can be any naturally occurring amino acid

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<223>  Xaa can be any naturally occurring amino acid

<400>  15

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Asn
            20                  25                  30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
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Gly Thr Ile Ser Gly Ser Gly Gly Ser Thr Xaa Tyr Xaa Xaa Xaa Xaa
    50                  55                  60

Xaa Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Thr Ser Ser Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210>  16
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<223>  Xaa: diversified position

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<223>  Xaa can be any naturally occurring amino acid

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<222>  (56)..(59)
<223>  Xaa can be any naturally occurring amino acid

<400>  16

Ser Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Thr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Xaa Gly Asn Asn Xaa Arg Xaa Xaa Xaa Xaa Pro Asp Arg Phe Ser
    50                  55                  60
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Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95

Asn Gly Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 17
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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (106)..(106)
<223> Xaa can be any naturally occurring amino acid

<400> 17

Xaa Xaa Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Xaa Xaa Xaa Ser Xaa Xaa
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Thr Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Asn Asp Asn Val
50 55 60

Leu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Xaa Thr Xaa Xaa Gly Xaa Phe Asp Xaa Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 18
<211> 108
<212> PRT
<213> Artificial

<220>
<223> synthetic Vkappa domain

<400> 18

Gly Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Trp Tyr Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Lys Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Glu Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 19
<211> 108
<212> PRT
<213> Artificial

<220>
<223> synthetic Vkappa domain

<400> 19

Asp Thr Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Phe Ala Ala Ser Arg Leu Ile Leu Asn Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 20
<211> 108
<212> PRT
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<220>
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<400> 20

Gly Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Trp Tyr Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Phe Ala Ala Ser Arg Leu Ile Leu Asn Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Lys Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Glu Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 21
<211> 116
<212> PRT
<213> Artificial

<220>
<223> synthetic VH domain

<400> 21

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Gln Ile Ser Gly Ser Gly Gly Ser Thr Trp Tyr Asn His Asp Ile
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ser Gly Tyr Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 22
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<212> PRT
<213> Artificial

<220>
<223> synthetic VH domain

<400> 22

Trp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Arg Gly Phe Pro Phe Ser His Tyr
20 25 30

Ala Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Gln Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Asn Asp Asn Val
50 55 60

Leu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ser Gly Tyr Phe Asp Trp Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 23
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<212> PRT
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<220>
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<400> 23

Trp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Arg Gly Phe Pro Phe Ser His Tyr
20 25 30

Ala Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Gln Ile Ser Gly Ser Gly Gly Ser Thr Trp Tyr Asn His Asp Ile
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ser Gly Tyr Phe Asp Trp Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 24
<211> 108
<212> PRT
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<220>

<223> synthetic Vkappa domain

<400> 24

Asn Ile Gln Lys Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Leu Trp His Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Gly Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 25
<211> 108
<212> PRT
<213> Artificial

<220>
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<400> 25

Asp Thr Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser His Leu His Tyr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 26
<211> 108
<212> PRT
<213> Artificial

<220>
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<400> 26

Asn Ile Gln Lys Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Leu Trp His Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser His Leu His Tyr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Gly Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 27
<211> 116
<212> PRT
<213> Artificial

<220>
<223> synthetic VH domain

<400> 27

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Gln Ile Ser Gly Ser Gly Gly Ser Thr Val Tyr Asn Tyr Asn Val
50 55 60

Leu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ser Gly Tyr Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 28
<211> 116
<212> PRT
<213> Artificial

<220>
<223> synthetic VH domain

<400> 28

Tyr Tyr Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Asp Gly Phe Leu Phe Ser Gly Tyr
20 25 30

Ala Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Gln Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Asn Asp Asn Val
50 55 60

Leu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Gly Tyr Phe Asp His Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 29
<211> 116
<212> PRT
<213> Artificial

<220>
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<400> 29

Tyr Tyr Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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Ser Leu Arg Leu Ser Cys Ala Ala Asp Gly Phe Leu Phe Ser Gly Tyr
            20                  25                  30

Ala Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Gln Ile Ser Gly Ser Gly Gly Ser Thr Val Tyr Asn Tyr Asn Val
    50                  55                  60

Leu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Thr Gly Tyr Phe Asp His Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser
        115


<210>  30
<211>  108
<212>  PRT
<213>  Artificial

<220>
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<400>  30

Ala Thr Gln Arg Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Leu Trp His Ile Ser Ser Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Trp Leu Tyr Trp Asp Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Gly Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100                 105
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<210> 31
<211> 116
<212> PRT
<213> Artificial

<220>
<223> synthetic VH domain

<400> 31

Trp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Lys Gly Ala Leu Phe Ser Thr Tyr
20 25 30

Ala Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Gln Ile Ser Gly Ser Gly Gly Ser Thr Val Tyr Asn Tyr Asn Val
50 55 60

Leu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ser Gly Tyr Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115