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(54) Title: MULTISPECIFIC ANTIBODY MOLECULES COMPRISING LAMBDA AND KAPPA LIGHT CHAINS

(57) Abstract: Multispecific, e.g., bispecific, antibody molecules that include a kappa light chain polypeptide and one lambda light chain polypeptide, and methods of making and using the multispecific antibody molecules, are disclosed.

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MULTISPECIFIC ANTIBODY MOLECULES COMPRISING LAMBDA AND KAPPA LIGHT CHAINS

This application claims priority to U.S. Serial No. 62/399,319 filed September 23, 2016, and U.S. Serial No. 62/474,569 filed March 21, 2017, the contents of which are incorporated herein by reference in their entireties.

BACKGROUND

Multispecific, e.g., bispecific, antibody molecules that include a lambda chain polypeptide and a kappa light chain polypeptide, and methods of making and using the same, are disclosed.

Mispairing of the light chains to the incorrect heavy chain, also known as light chain shuffling, is a problem frequently observed when preparing bispecific and other multispecific antibodies. This results in the formation of incorrect antibody pairings, leading to decreased production yield. Thus, the need exists to develop methods and compositions that reduce light chain shuffling.

SUMMARY OF THE INVENTION

The present application is based, at least in part, on the unexpected finding that light chain shuffle in the context of a multispecific antibody molecule, *e.g.*, a bispecific IgG molecule, can be prevented by using one kappa light chain polypeptide and one lambda light chain polypeptide. This is based, in part, on the observation that kappa light chains do not pair with a heavy chain from a lambda antibody and vice versa. Thus, described herein are novel multispecific, e.g., bispecific, antibody molecules that include a kappa light chain polypeptide and a lambda light chain polypeptide, and methods of making and using the multispecific antibody molecules.

Accordingly, in one aspect, disclosed herein is a multispecific antibody molecule, e.g., an antibody molecule comprising two binding specificities, e.g., a bispecific antibody molecule. The multispecific antibody molecule comprises:

i) a first antigen-binding domain that binds to a first antigen, wherein the first antigen-binding domain comprises:

a) a first heavy chain polypeptide (HCP1) comprising: a first heavy chain variable region sequence (HCVRS) sufficient that, when paired with i)b) allows the first antigen-binding domain to bind to the first antigen; and

b) a lambda light chain polypeptide (LLCP) comprising: a lambda light chain variable region sequence (LLCVRS) sufficient that, when paired with i)a) allows the first antigen-binding domain to bind to the first antigen; and

ii) a second antigen-binding domain that binds to a second antigen, wherein the second antigen-binding domain comprises:

a) a second heavy chain polypeptide (HCP2) comprising: a second heavy chain variable region sequence (HCVRS) sufficient that, when paired with ii)b) allows the second antigen-binding domain to bind to the second antigen; and

b) a kappa light chain polypeptide (KLCP) comprising: a kappa light chain variable region sequence (KLCVRS) sufficient that, when paired with ii)a) allows the second antigen-binding domain to bind to the second antigen.

In one embodiment, the first HCVRS comprises one, two, or all of framework 1 sequence, framework 2 sequence, or framework 3 sequence. In one embodiment, the framework 1 sequence, framework 2 sequence, or framework 3 sequence of the first HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a corresponding region in a first heavy chain germline sequence selected from column 3 of Table 7, column 2 of Table 8b, or column 2 of Table 5b. In one embodiment, the framework 1 sequence, framework 2 sequence, or framework 3 sequence of the first HCVRS comprises no more than 1, 2, 3, 4, 5, 6, 7, or 8 amino acid mutations (e.g., substitutions, insertions, or deletions, e.g., conserved substitutions) relative to a corresponding region in a first heavy chain germline sequence selected from column 3 of Table 7, column 2 of Table 8b, or column 2 of Table 5b. In one embodiment, the first HCVRS comprises a framework sequence selected from Table 16.

In one embodiment, the LLCVRS comprises one, two, or all of framework 1 sequence, framework 2 sequence, or framework 3 sequence. In one embodiment, the framework 1 sequence, framework 2 sequence, or framework 3 sequence of the LLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a corresponding region in a lambda light chain germline sequence selected from column 4 of Table 7, column 3 of Table 8b; or column 3 of

Table 5b. In one embodiment, the framework 1 sequence, framework 2 sequence, or framework 3 sequence of the LLCVRS comprises no more than 1, 2, 3, 4, 5, 6, 7, or 8 amino acid mutations (e.g., substitutions, insertions, or deletions, e.g., conserved substitutions) relative to a corresponding region in a lambda light chain germline sequence selected from column 4 of Table 7, column 3 of Table 8b; or column 3 of Table 5b. In one embodiment, the LLCVRS comprises a framework sequence selected from Table 16.

In one embodiment, the second HCVRS comprises one, two, or all of framework 1 sequence, framework 2 sequence, or framework 3 sequence. In one embodiment, the framework 1 sequence, framework 2 sequence, or framework 3 sequence of the first HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a corresponding region in a second heavy chain germline sequence selected from column 3 of Table 6, column 5 of Table 8b, or column 4 of Table 5b. In one embodiment, the framework 1 sequence, framework 2 sequence, or framework 3 sequence of the second HCVRS comprises no more than 1, 2, 3, 4, 5, 6, 7, or 8 amino acid mutations (e.g., substitutions, insertions, or deletions, e.g., conserved substitutions) relative to a corresponding region in a second heavy chain germline sequence selected from column 3 of Table 6, column 5 of Table 8b, or column 4 of Table 5b. In one embodiment, the second HCVRS comprises a framework sequence selected from Table 16.

In one embodiment, the KLCVRS comprises one, two, or all of framework 1 sequence, framework 2 sequence, or framework 3 sequence. In one embodiment, the framework 1 sequence, framework 2 sequence, or framework 3 sequence of the LLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a corresponding region in a kappa light chain germline sequence selected from column 4 of Table 6, column 6 of Table 8b, or column 5 of Table 5b. In one embodiment, the framework 1 sequence, framework 2 sequence, or framework 3 sequence of the KLCVRS comprises no more than 1, 2, 3, 4, 5, 6, 7, or 8 amino acid mutations (e.g., substitutions, insertions, or deletions, e.g., conserved substitutions) relative to a corresponding region in a kappa light chain germline sequence selected from column 4 of Table 6, column 6 of Table 8b, or column 5 of Table 5b. In one embodiment, the KLCVRS comprises a framework sequence selected from Table 16.

In one embodiment, 1) the first HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a first heavy chain germline sequence selected from column 3 of Table 7,

column 2 of Table 8b, or column 2 of Table 5b; 2) the LLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a lambda light chain germline sequence selected from column 4 of Table 7, column 3 of Table 8b; or column 3 of Table 5b; 3) the second HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a second heavy chain germline sequence selected from column 3 of Table 6, column 5 of Table 8b, or column 4 of Table 5b; or 4) the KLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a kappa light chain germline sequence selected from column 4 of Table 6, column 6 of Table 8b, or column 5 of Table 5b.

In one embodiment, the first HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a first heavy chain germline sequence selected from column 3 of Table 7, column 2 of Table 8b, or column 2 of Table 5b. In one embodiment, the first heavy chain germline sequence and the lambda light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b. In one embodiment, the first heavy chain germline sequence, the lambda light chain germline sequence, and the kappa light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b. In one embodiment, the second heavy chain germline sequence and the kappa light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b. In one embodiment, the second heavy chain germline sequence, the kappa light chain germline sequence, and the lambda light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b. In one embodiment, at least two (e.g., two, three, or all) of the following: the first heavy chain germline sequence, the lambda light chain germline sequence, the second heavy chain germline sequence, and the kappa light chain germline sequence, are selected from a single row of Table 8b or Table 5b.

In one embodiment, the LLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a lambda light chain germline sequence selected from column 4 of Table 7, column 3 of Table 8b; or column 3 of Table 5b. In one embodiment, the first heavy chain germline sequence and the lambda light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b. In one embodiment, the first heavy chain germline sequence, the lambda light chain germline sequence, and the kappa light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b. In one embodiment, the second heavy chain

germline sequence and the kappa light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b. In one embodiment, the second heavy chain germline sequence, the kappa light chain germline sequence, and the lambda light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b. In one embodiment, at least two (e.g., two, three, or all) of the following: the first heavy chain germline sequence, the lambda light chain germline sequence, the second heavy chain germline sequence, and the kappa light chain germline sequence, are selected from a single row of Table 8b or Table 5b.

In one embodiment, the second HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a second heavy chain germline sequence selected from column 3 of Table 6, column 5 of Table 8b, or column 4 of Table 5b. In one embodiment, the first heavy chain germline sequence and the lambda light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b. In one embodiment, the first heavy chain germline sequence, the lambda light chain germline sequence, and the kappa light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b. In one embodiment, the second heavy chain germline sequence and the kappa light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b. In one embodiment, the second heavy chain germline sequence, the kappa light chain germline sequence, and the lambda light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b. In one embodiment, at least two (e.g., two, three, or all) of the following: the first heavy chain germline sequence, the lambda light chain germline sequence, the second heavy chain germline sequence, and the kappa light chain germline sequence, are selected from a single row of Table 8b or Table 5b.

In one embodiment, the KLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a kappa light chain germline sequence selected from column 4 of Table 6, column 6 of Table 8b, or column 5 of Table 5b. In one embodiment, the first heavy chain germline sequence and the lambda light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b. In one embodiment, the first heavy chain germline sequence, the lambda light chain germline sequence, and the kappa light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b. In one embodiment, the second heavy chain germline sequence and the kappa light chain germline sequence are selected from a single row of

Table 6, Table 8b, or Table 5b. In one embodiment, the second heavy chain germline sequence, the kappa light chain germline sequence, and the lambda light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b. In one embodiment, at least two (e.g., two, three, or all) of the following: the first heavy chain germline sequence, the lambda light chain germline sequence, the second heavy chain germline sequence, and the kappa light chain germline sequence, are selected from a single row of Table 8b or Table 5b.

In one embodiment, the first heavy chain germline sequence and the lambda light chain germline sequence are selected from a single row of Table 8b or Table 5b. In one embodiment, the first heavy chain germline sequence and the second heavy chain germline sequence are selected from a single row of Table 8b or Table 5b. In one embodiment, the first heavy chain germline sequence and the kappa light chain germline sequence are selected from a single row of Table 8b or Table 5b. In one embodiment, the lambda light chain germline sequence and the second heavy chain germline sequence are selected from a single row of Table 8b or Table 5b. In one embodiment, the lambda light chain germline sequence and the kappa light chain germline sequence are selected from a single row of Table 8b or Table 5b. In one embodiment, the second heavy chain germline sequence and the kappa light chain germline sequence are selected from a single row of Table 8b or Table 5b. In one embodiment, the first heavy chain germline sequence, the lambda light chain germline sequence, and the second heavy chain germline sequence are selected from a single row of Table 8b or Table 5b. In one embodiment, the first heavy chain germline sequence, the lambda light chain germline sequence, and the kappa light chain germline sequence are selected from a single row of Table 8b or Table 5b. In one embodiment, the first heavy chain germline sequence, the second heavy chain germline sequence, and the kappa light chain germline sequence are selected from a single row of Table 8b or Table 5b. In one embodiment, the lambda light chain germline sequence, the second heavy chain germline sequence, and the kappa light chain germline sequence are selected from a single row of Table 8b or Table 5b. In one embodiment, the first heavy chain germline sequence, the lambda light chain germline sequence, the second heavy chain germline sequence, and the kappa light chain germline sequence are selected from a single row of Table 8b or Table 5b.

In certain embodiments of the foregoing aspects, the multispecific antibody molecule further comprises an accessory moiety, wherein the accessory moiety has a property chosen from:

1) the accessory moiety has a molecular weight of at least 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 kDa;

2) the accessory moiety comprises a polypeptide having at least 30, 40, 50, 60, 70, 80, 90, or 100 amino acid residues;

3) the accessory moiety comprises a polypeptide having the ability to modulate the activity of an immune cell, e.g., a T cell, a B cell, an antigen presenting cell (APC), or an NK cell; or

4) the accessory moiety is chosen from one or more of an immune cell engager (e.g., a CD40 agonist, e.g., a CD40L polypeptide or an agonistic anti-CD40 antibody molecule, or a PD-1 binding moiety, e.g., a PD-1 binding sequence of PDL-1 or an anti-PD-1 antibody molecule), a cytokine molecule (e.g. an IL-2 molecule), a cytokine antagonist (e.g., a TGF-β antagonist), an enzyme, a toxin, or a labeling agent.

In one aspect, disclosed herein is a multispecific antibody molecule comprising:

i) a first antigen-binding domain that binds to a first antigen, wherein the first antigen-binding domain comprises:

a) a first heavy chain polypeptide (HCP1) comprising: a first heavy chain variable region sequence (HCVRS) sufficient that, when paired with i)b) allows the first antigen-binding domain to bind to the first antigen; and

b) a lambda light chain polypeptide (LLCP) comprising: a lambda light chain variable region sequence (LLCVRS) sufficient that, when paired with i)a) allows the first antigen-binding domain to bind to the first antigen; and

ii) a second antigen-binding domain that binds to a second antigen, wherein the second antigen-binding domain comprises:

a) a second heavy chain polypeptide (HCP2) comprising: a second heavy chain variable region sequence (HCVRS) sufficient that, when paired with ii)b) allows the second antigen-binding domain to bind to the second antigen; and

b) a kappa light chain polypeptide (KLCP) comprising: a kappa light chain variable region sequence (KLCVRS) sufficient that, when paired with ii)a) allows the second antigen-binding domain to bind to the second antigen, wherein:

the multispecific antibody molecule further comprises an accessory moiety, wherein the accessory moiety has a property chosen from:

1) the accessory moiety has a molecular weight of at least 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 kDa;

2) the accessory moiety comprises a polypeptide having at least 30, 40, 50, 60, 70, 80, 90, or 100 amino acid residues;

3) the accessory moiety comprises a polypeptide having the ability to modulate the activity of an immune cell, e.g., a T cell, a B cell, an antigen presenting cell (APC), or an NK cell; or

4) the accessory moiety is chosen from one or more of an immune cell engager (e.g., a CD40 agonist, e.g., a CD40L polypeptide or an agonistic anti-CD40 antibody molecule, or a PD-1 binding moiety, e.g., a PD-1 binding sequence of PDL-1 or an anti-PD-1 antibody molecule), a cytokine molecule (e.g. an IL-2 molecule), a cytokine antagonist (e.g., a TGF-β antagonist), an enzyme, a toxin, or a labeling agent.

Exemplary multispecific antibody molecules with one or more accessory moieties are shown in FIGs. 6-10 and described in Examples (e.g., multispecific molecule 8 described in Example 9, multispecific molecule 9 described in Example 10, multispecific molecule 10 described in Example 11, multispecific molecule 11 described in Example 12, multispecific molecule 12 described in Example 13).

In one embodiment, the accessory moiety has a molecular weight of at least 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 kDa. In one embodiment, the accessory moiety comprises a polypeptide having at least 30, 40, 50, 60, 70, 80, 90, or 100 amino acid residues. In one embodiment, the accessory moiety comprises a polypeptide having the ability to modulate the activity of an immune cell, e.g., a T cell, a B cell, an antigen presenting cell (APC), or an NK cell. In one embodiment, the accessory moiety is chosen from one or more of an immune cell engager (e.g., a CD40 agonist, e.g., a CD40L polypeptide or an agonistic anti-CD40 antibody molecule, or a PD-1 binding moiety, e.g., a PD-1 binding sequence of PDL-1 or an anti-PD-1

antibody molecule), a cytokine molecule (e.g. an IL-2 molecule), a cytokine antagonist (e.g., a TGF-β antagonist), an enzyme, a toxin, or a labeling agent.

In one embodiment, the accessory moiety is fused to the polypeptide of a , b, c, or d of the multispecific antibody molecule. In one embodiment, the accessory moiety is fused to any of the following: the HCP1, first HCVRS, LLCP, LLCVRS, HCP2, second HCVRS, KLCP, or KLCVRS of the multispecific antibody molecule, e.g., the C-terminus or N-terminus of HCP1, first HCVRS, LLCP, LLCVRS, HCP2, second HCVRS, KLCP, or KLCVRS of the multispecific antibody molecule. In one embodiment, the accessory moiety is fused to the HCP1. In one embodiment, the accessory moiety is fused to the first HCVRS (e.g., the C-terminus or N-terminus of the first HCVRS). In one embodiment, the accessory moiety is fused to the LLCP (e.g., the C-terminus or N-terminus of the LLCP). In one embodiment, the accessory moiety is fused to the LLCVRS (e.g., the C-terminus or N-terminus of the LLCVRS). In one embodiment, the accessory moiety is fused to the HCP2 (e.g., the C-terminus or N-terminus of the HCP2). In one embodiment, the accessory moiety is fused to the second HCVRS (e.g., the C-terminus or N-terminus of the second HCVRS). In one embodiment, the accessory moiety is fused to the KLCP (e.g., the C-terminus or N-terminus of the KLCP). In one embodiment, the accessory moiety is fused to the KLCVRS (e.g., the C-terminus or N-terminus of the KLCVRS). In one embodiment, the HCP1 comprises a first heavy chain constant region sequence (HCCRS) (e.g., CH1, CH2, and CH3 sequences), wherein the accessory moiety is fused to the first HCCRS, e.g., the C-terminus of the first HCCRS. In one embodiment, the HCP2 comprises a second heavy chain constant region sequence (HCCRS) (e.g., CH1, CH2, and CH3 sequences), wherein the accessory moiety is fused to the second HCCRS, e.g., the C-terminus of the second HCCRS. In one embodiment, the LLCP comprises a lambda light chain constant region sequence (LLCCRS), wherein the accessory moiety is fused to the LLCCRS, e.g., the C-terminus of the LLCCRS. In one embodiment, the KLCP comprises a kappa light chain constant region sequence (KLCCRS), wherein the accessory moiety is fused to the KLCCRS, e.g., the C-terminus of the KLCCRS.

In one embodiment, the multispecific antibody molecule comprises one or more (e.g., two, three, four, five, or more) accessory molecule. In one embodiment, the multispecific antibody molecule comprises a first accessory moiety and a second accessory moiety, wherein the first or second accessory moiety has a property chosen from:

1) the first or second accessory moiety has a molecular weight of at least 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 kDa;

2) the first or second accessory moiety comprises a polypeptide having at least 30, 40, 50, 60, 70, 80, 90, or 100 amino acid residues;

3) the first or second accessory moiety comprises a polypeptide having the ability to modulate the active of an immune cell, e.g., a T cell, a B cell, an antigen presenting cell (APC), or an NK cell; or

4) the first or second accessory moiety is chosen from one or more of an immune cell engager (e.g., a CD40 agonist, e.g., a CD40L polypeptide or an agonistic anti-CD40 antibody molecule, or a PD-1 binding moiety, e.g., a PD-1 binding sequence of PDL-1 or an anti-PD-1 antibody molecule), a cytokine molecule (e.g. an IL-2 molecule), a cytokine antagonist (e.g., a TGF-β antagonist), an enzyme, a toxin, or a labeling agent.

In one embodiment, the first and second accessory moieties are the same. In one embodiment, the first and second accessory moieties are different. In one embodiment, i) the first accessory moiety is fused to the HCP1 or HCP2, e.g., the C-terminus of the HCP1 or HCP2; and ii) the second accessory moiety is fused to the LLCP or KLCP, e.g., the C-terminus of the LLCP or KLCP. In one embodiment, i) the first accessory moiety is fused to the HCP1, e.g., the C-terminus of the HCP1; and ii) the second accessory moiety is fused to the LLCP, e.g., the C-terminus of the LLCP. In one embodiment, i) the first accessory moiety is fused to the HCP1, e.g., the C-terminus of the HCP1; and ii) the second accessory moiety is fused to the KLCP, e.g., the C-terminus of the KLCP. In one embodiment, i) the first accessory moiety is fused to the HCP2, e.g., the C-terminus of the HCP2; and ii) the second accessory moiety is fused to the LLCP, e.g., the C-terminus of the LLCP. In one embodiment, i) the first accessory moiety is fused to the HCP2, e.g., the C-terminus of the HCP2; and ii) the second accessory moiety is fused to the KLCP, e.g., the C-terminus of the KLCP. In one embodiment, i) the first accessory moiety is fused to the KLCP, e.g., the C-terminus of the KLCP; and ii) the second accessory moiety is fused to the LLCP, e.g., the C-terminus of the LLCP. In one embodiment, i) the first accessory moiety is fused to the LLCP, e.g., the C-terminus of the LLCP; and ii) the second accessory moiety is fused to the KLCP, e.g., the C-terminus of the KLCP. In one embodiment, i) the HCP1 comprises a first heavy chain constant region sequence (HCCRS) (e.g., CH1, CH2, and CH3 sequences), wherein the first accessory moiety is fused to the first HCCRS, e.g., the C-

terminus of the first HCCRS; and ii) the LLCP comprises a lambda light chain constant region sequence (LLCCRS), wherein the second accessory moiety is fused to the LLCCRS, e.g., the C-terminus of the LLCCRS. In one embodiment, i) the HCP2 comprises a second heavy chain constant region sequence (HCCRS) (e.g., CH1, CH2, and CH3 sequences), wherein the accessory moiety is fused to the second HCCRS, e.g., the C-terminus of the second HCCRS; and ii) the KLCP comprises a kappa light chain constant region sequence (KLCCRS), wherein the accessory moiety is fused to the KLCCRS, e.g., the C-terminus of the KLCCRS. In one embodiment, i) the HCP1 comprises a first heavy chain constant region sequence (HCCRS) (e.g., CH1, CH2, and CH3 sequences), wherein the first accessory moiety is fused to the first HCCRS, e.g., the C-terminus of the first HCCRS; and ii) the KLCP comprises a kappa light chain constant region sequence (KLCCRS), wherein the accessory moiety is fused to the KLCCRS, e.g., the C-terminus of the KLCCRS. In one embodiment, i) the HCP2 comprises a second heavy chain constant region sequence (HCCRS) (e.g., CH1, CH2, and CH3 sequences), wherein the accessory moiety is fused to the second HCCRS, e.g., the C-terminus of the second HCCRS; and ii) the LLCP comprises a lambda light chain constant region sequence (LLCCRS), wherein the second accessory moiety is fused to the LLCCRS, e.g., the C-terminus of the LLCCRS.

In certain embodiments of the foregoing aspects, the multispecific antibody molecule comprises:

i)a) the HCP1 comprises a first heavy chain constant region sequence (HCCRS) (e.g., a first CH1 sequence),

i)b) the LLCP comprises a lambda light chain constant region sequence (LLCCRS),

ii)a) the HCP2 comprises a second heavy chain constant region sequence (HCCRS) (e.g., a second CH1 sequence), and

ii)b) the KLCP comprises a kappa light chain constant region sequence (KLCCRS), wherein:

1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation, or the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light

chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation; and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation, or the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation.

In one aspect, disclosed herein is a multispecific antibody comprising:

i) a first antigen-binding domain that binds to a first antigen, wherein the first antigen-binding domain comprises:

a) a first heavy chain polypeptide (HCP1) comprising: a first heavy chain variable region sequence (HCVRS) sufficient that, when paired with i)b) allows the first antigen-binding domain to bind to the first antigen; and a first heavy chain constant region sequence (HCCRS) (e.g., a first CH1 sequence), and

b) a lambda light chain polypeptide (LLCP) comprising: a lambda light chain variable region sequence (LLCVRS) sufficient that, when paired with i)a) allows the first antigen-binding domain to bind to the first antigen; and a lambda light chain constant region sequence (LLCCRS), and

ii) a second antigen-binding domain that binds to a second antigen, wherein the second antigen-binding domain comprises:

a) a second heavy chain polypeptide (HCP2) comprising: a second heavy chain variable region sequence (HCVRS) sufficient that, when paired with ii)b) allows the second antigen-binding domain to bind to the second antigen; and a second heavy chain constant region sequence (HCCRS) (e.g., a second CH1 sequence) and

b) a kappa light chain polypeptide (KLCP) comprising: a kappa light chain variable region sequence (KLCVRS) sufficient that, when paired with ii)a) allows the second antigen-binding domain to bind to the second antigen; and a kappa light chain constant region sequence (KLCCRS), wherein:

1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation, or the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation; and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation, or the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation.

In one embodiment, 1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation; and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation.

In one embodiment, 1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation; and

2) the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation.

In one embodiment, 1) the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation; and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation.

In one embodiment, 1) the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation; and

2) the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation.

In one embodiment, 1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation, and the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation; and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation, or the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation.

In one embodiment, 1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation, or the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation; and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation, and the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation.

In one embodiment, 1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation, and the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation; and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation, and the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation.

In one embodiment, the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that increases the preferential pairing of the HCP1 and the LLCP by at least 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or 50 folds, compared with pairing of the HCP1 and the LLCP without the mutation. In one embodiment, the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence) that increases the preferential pairing of the HCP1 and the LLCP by at least 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or 50 folds, compared with pairing of the HCP1 and the LLCP without the mutation.

In one embodiment, the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that increases the preferential pairing of the HCP2 and the KLCP by at least 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or 50 folds, compared with pairing of the HCP2 and the KLCP without the mutation. In one embodiment, the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence) that increases the preferential pairing of the HCP2 and the KLCP by at least 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or 50 folds, compared with pairing of the HCP2 and the KLCP without the mutation.

In certain embodiments of the foregoing aspects, the multispecific antibody molecule comprises:

i)a) the HCP1 comprises a first heavy chain constant region sequence (HCCRS) (e.g., a first CH1 sequence),

i)b) the LLCP comprises a lambda light chain constant region sequence (LLCCRS),

ii)a) the HCP2 comprises a second heavy chain constant region sequence (HCCRS) (e.g., a second CH1 sequence), and

ii)b) the KLCP comprises a kappa light chain constant region sequence (KLCCRS), wherein:

1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence),

or the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence); and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence), or the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence).

In one aspect, disclosed herein is a multispecific antibody comprising:

i) a first antigen-binding domain that binds to a first antigen, wherein the first antigen-binding domain comprises:

a) a first heavy chain polypeptide (HCP1) comprising: a first heavy chain variable region sequence (HCVRS) sufficient that, when paired with i)b) allows the first antigen-binding domain to bind to the first antigen; and a first heavy chain constant region sequence (HCCRS) (e.g., a first CH1 sequence), and

b) a lambda light chain polypeptide (LLCP) comprising: a lambda light chain variable region sequence (LLCVRS) sufficient that, when paired with i)a) allows the first antigen-binding domain to bind to the first antigen; and a lambda light chain constant region sequence (LLCCRS), and

ii) a second antigen-binding domain that binds to a second antigen, wherein the second antigen-binding domain comprises:

a) a second heavy chain polypeptide (HCP2) comprising: a second heavy chain variable region sequence (HCVRS) sufficient that, when paired with ii)b) allows the second antigen-binding domain to bind to the second antigen; and a second heavy chain constant region sequence (HCCRS) (e.g., a second CH1 sequence) and

b) a kappa light chain polypeptide (KLCP) comprising: a kappa light chain variable region sequence (KLCVRS) sufficient that, when paired with ii)a) allows the second antigen-binding domain to bind to the second antigen; and a kappa light chain constant region sequence (KLCCRS), wherein:

1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence),

or the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence); and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence), or the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence).

In one embodiment, the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence), and the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence).

In one embodiment, the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence), and the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence).

In one embodiment, the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence), and the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence).

In one embodiment, the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence), and the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence).

In one embodiment,

1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence), and the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence); and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence),

or the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence).

In one embodiment,

1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence), or the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence); and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence), and the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence).

In one embodiment,

1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence), and the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence); and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence), and the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence).

In one embodiment, the multispecific antibody molecule does not comprise a mutation in any of the following: the first HCCRS, the LLCCRS, the second HCCRS, and the KLCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence, a naturally existing lambda light chain constant region sequence, or a naturally existing kappa light chain constant region sequence).

In one embodiment, the multispecific antibody molecule does not comprise a mutation disclosed in WO2017059551.

In certain embodiments of the foregoing aspects, the multispecific antibody molecule comprises:

i)a) the HCP1 comprises a first heavy chain constant region sequence (HCCRS) (e.g., a first CH1 sequence),

i)b) the LLCP comprises a lambda light chain constant region sequence (LLCCRS),

ii)a) the HCP2 comprises a second heavy chain constant region sequence (HCCRS) (e.g., a second CH1 sequence) and

ii)b) the KLCP comprises a kappa light chain constant region sequence (KLCCRS), wherein:

1) the first HCCRS comprises a naturally existing heavy chain constant region sequence, or the LLCCRS comprises a naturally existing lambda light chain constant region sequence; and

2) the second HCCRS comprises a naturally existing heavy chain constant region sequence, or the KLCCRS comprises a naturally existing kappa light chain constant region sequence.

In one aspect, disclosed herein is a multispecific antibody molecule comprising:

i) a first antigen-binding domain that binds to a first antigen, wherein the first antigen-binding domain comprises:

a) a first heavy chain polypeptide (HCP1) comprising: a first heavy chain variable region sequence (HCVRS) sufficient that, when paired with i)b) allows the first antigen-binding domain to bind to the first antigen; and a first heavy chain constant region sequence (HCCRS) (e.g., a first CH1 sequence), and

b) a lambda light chain polypeptide (LLCP) comprising: a lambda light chain variable region sequence (LLCVRS) sufficient that, when paired with i)a) allows the first antigen-binding domain to bind to the first antigen; and a lambda light chain constant region sequence (LLCCRS), and

ii) a second antigen-binding domain that binds to a second antigen, wherein the second antigen-binding domain comprises:

a) a second heavy chain polypeptide (HCP2) comprising: a second heavy chain variable region sequence (HCVRS) sufficient that, when paired with ii)b) allows the second antigen-binding domain to bind to the second antigen; and a second heavy chain constant region sequence (HCCRS) (e.g., a second CH1 sequence) and

b) a kappa light chain polypeptide (KLCP) comprising: a kappa light chain variable region sequence (KLCVRS) sufficient that, when paired with ii)a) allows the second antigen-binding domain to bind to the second antigen; and a kappa light chain constant region sequence (KLCCRS), wherein:

1) the first HCCRS comprises a naturally existing heavy chain constant region sequence, or the LLCCRS comprises a naturally existing lambda light chain constant region sequence; and

2) the second HCCRS comprises a naturally existing heavy chain constant region sequence, or the KLCCRS comprises a naturally existing kappa light chain constant region sequence.

In one embodiment, 1) the first HCCRS comprises a naturally existing heavy chain constant region sequence; and 2) the second HCCRS comprises a naturally existing heavy chain constant region sequence. In one embodiment, 1) the first HCCRS comprises a naturally existing heavy chain constant region sequence; and 2) the KLCCRS comprises a naturally existing kappa light chain constant region sequence. In one embodiment, 1) the LLCCRS comprises a naturally existing lambda light chain constant region sequence; and 2) the second HCCRS comprises a naturally existing heavy chain constant region sequence. In one embodiment, 1) the LLCCRS comprises a naturally existing lambda light chain constant region sequence; and 2) the KLCCRS comprises a naturally existing kappa light chain constant region sequence. In one embodiment, 1) the first HCCRS comprises a naturally existing heavy chain constant region sequence, and the LLCCRS comprises a naturally existing lambda light chain constant region sequence; and 2) the second HCCRS comprises a naturally existing heavy chain constant region sequence, or the KLCCRS comprises a naturally existing kappa light chain constant region sequence. In one embodiment, 1) the first HCCRS comprises a naturally existing heavy chain constant region sequence, or the LLCCRS comprises a naturally existing lambda light chain constant region sequence; and 2) the second HCCRS comprises a naturally existing heavy chain constant region sequence, and the KLCCRS comprises a naturally existing kappa light chain constant region sequence.

In one embodiment, i) the first HCCRS comprises a naturally existing heavy chain constant region sequence, ii) the LLCCRS comprises a naturally existing lambda light chain constant region sequence, iii) the second HCCRS comprises a naturally existing heavy chain

constant region sequence, and iv) the KLCCRS comprises a naturally existing kappa light chain constant region sequence.

In certain embodiments of the foregoing aspects, the HCP1 preferentially binds to the LLCP over the KLCP. In certain embodiments of the foregoing aspects, the LLCP preferentially binds to the HCP1 over the HCP2. In certain embodiments of the foregoing aspects, the HCP2 preferentially binds to the KLCP over the LLCP. In certain embodiments of the foregoing aspects, the KLCP preferentially binds to the HCP2 over the HCP1. In one embodiment, the HCP1 has a higher affinity, e.g., a substantially higher affinity, for the LLCP than for the KLCP (e.g., the KD for the binding between the HCP1 and the LLCP is no more than 50%, 40%, 30%, 20%, 10%, 1%, 0.1%, or 0.01% of the KD for the binding between the HCP1 and the KLCP). In one embodiment, the LLCP has a higher affinity, e.g., a substantially higher affinity, for the HCP1 than for the HCP2 (e.g., the KD for the binding between the LLCP and the HCP1 is no more than 50%, 40%, 30%, 20%, 10%, 1%, 0.1%, or 0.01% of the KD for the binding between the LLCP and the first HCP2). In one embodiment, the HCP2 has a higher affinity, e.g., a substantially higher affinity, for the KLCP than for the LLCP (e.g., the KD for the binding between the HCP2 and the KLCP is no more than 50%, 40%, 30%, 20%, 10%, 1%, 0.1%, or 0.01% of the KD for the binding between the HCP2 and the LLCP). In one embodiment, the KLCP has a higher affinity, e.g., a substantially higher affinity, for the HCP2 than for the HCP1 (e.g., the KD for the binding between the KLCP and the HCP2 is no more than 50%, 40%, 30%, 20%, 10%, 1%, 0.1%, or 0.01% of the KD for the binding between the KLCP and the HCP1).

In one embodiment, the percent binding between the HCP1 and the LLCP in the presence of the KLCP is at least 75, 80, 90, 95, 98, 99, or 99.5%. In one embodiment, when the HCP1, LLCP, and KLCP are present at 1:1:1, the percent binding between the HCP1 and the LLCP in the presence of the KLCP is at least 75, 80, 90, 95, 98, 99, or 99.5% (setting the binding between the HCP1 and the LLCP in the absence of any competing peptide to 100%, and the binding between the HCP1 and the LLCP in the presence of LLCP to 50%). In one embodiment, the percent binding was measured by an assay described herein, e.g., the NanoBiT assay.

In one embodiment, the percent binding between the HCP1 and the LLCP in the presence of the HCP2 is at least 75, 80, 90, 95, 98, 99, or 99.5%. In one embodiment, when HCP1, LLCP, and HCP2 are present at 1:1:1, the percent binding between the HCP1 and the LLCP in the

presence of the HCP2 is at least 75, 80, 90, 95, 98, 99, or 99.5% (setting the binding between the HCP1 and the LLCP in the absence of any competing peptide to 100%, and the binding between the HCP1 and the LLCP in the presence of HCP1 to 50%). In one embodiment, the percent binding was measured by an assay described herein, e.g., the NanoBiT assay.

In one embodiment, the percent binding between the HCP2 and the KLCP in the presence of the LLCP is at least 75, 80, 90, 95, 98, 99, or 99.5%. In one embodiment, when HCP2, KLCP, and LLCP are present at 1:1:1, the percent binding between the HCP2 and the KLCP in the presence of the LLCP is at least 75, 80, 90, 95, 98, 99, or 99.5% (setting the binding between the HCP2 and the KLCP in the absence of any competing peptide to 100%, and the binding between the HCP2 and the KLCP in the presence of KLCP to 50%). In one embodiment, the percent binding was measured by an assay described herein, e.g., the NanoBiT assay.

In one embodiment, the percent binding between the HCP2 and the KLCP in the presence of the HCP1 is at least 75, 80, 90, 95, 98, 99, or 99.5%. In one embodiment, when HCP2, KLCP, and HCP1 are present at 1:1:1, the percent binding between the HCP2 and the KLCP in the presence of the HCP1 is at least 75, 80, 90, 95, 98, 99, or 99.5% (setting the binding between the HCP2 and the KLCP in the absence of any competing peptide to 100%, and the binding between the HCP2 and the KLCP in the presence of HCP2 to 50%). In one embodiment, the percent binding was measured by an assay described herein, e.g., the NanoBiT assay.

In one embodiment, when the HCP1, LLCP, HCP2, and KLCP are present under preselected conditions, e.g., in aqueous buffer, e.g., at pH 7, in saline, e.g., at pH 7, or under physiological conditions: at least 70, 75, 80, 90, 95, 98, 99, 99.5, or 99.9 % of the HCP1 is complexed, or interfaced with, the LLCP. In one embodiment, when the HCP1, LLCP, HCP2, and KLCP are present under preselected conditions, e.g., in aqueous buffer, e.g., at pH 7, in saline, e.g., at pH 7, or under physiological conditions: at least 70, 75, 80, 90, 95, 98, 99, 99.5, or 99.9 % of the LLCP is complexed, or interfaced with, the HCP1. In one embodiment, when the HCP1, LLCP, HCP2, and KLCP are present under preselected conditions, e.g., in aqueous buffer, e.g., at pH 7, in saline, e.g., at pH 7, or under physiological conditions: at least 70, 75, 80, 90, 95, 98, 99, 99.5, or 99.9 % of the HCP2 is complexed, or interfaced with, the KLCP. In one embodiment, when the HCP1, LLCP, HCP2, and KLCP are present under preselected conditions, e.g., in aqueous buffer, e.g., at pH 7, in saline, e.g., at pH 7, or under physiological

conditions: at least 70, 75, 80, 90, 95, 98, 99, 99.5, or 99.9 % of the KLCP is complexed, or interfaced with, the HCP2.

In certain embodiments of the foregoing aspects, the multispecific antibody molecule comprises:

i)a) the HCP1 comprises a first heavy chain constant region sequence (HCCRS) (e.g., a first CH1 sequence),

i)b) the LLCP comprises a lambda light chain constant region sequence (LLCCRS),

ii)a) the HCP2 comprises a second heavy chain constant region sequence (HCCRS) (e.g., a second CH1 sequence) and

ii)b) the KLCP comprises a kappa light chain constant region sequence (KLCCRS), wherein:

1) the first HCCRS is complexed, or interfaced with, LLCCRS, and

2) the second HCCRS is complexed, or interfaced with, KLCCRS.

In certain embodiments of the foregoing aspects, the HCP1 is complexed, or interfaced with, the HCP2. In one embodiment, the HCP1 has a greater affinity, e.g., a substantially greater affinity, for HCP2, than for a second molecule of HCP1. In one embodiment, the HCP2 has a greater affinity, e.g., a substantially greater affinity, for HCP1, than for a second molecule of HCP2. In one embodiment, the HCP1 comprises a sequence element that increases the ratio of HCP1-HCP2: HCP1-HCP1 pairings, compared to the ratio that would be seen in the absence of the sequence element, e.g., where a naturally occurring sequence replaces the sequence element. In one embodiment, the HCP2 comprises a sequence element that increases the ratio of HCP1-HCP2: HCP2-HCP2 pairings, compared to the ratio that would be seen in the absence of the sequence element, e.g., where a naturally occurring sequence replaces the sequence element. In one embodiment, the sequence element is not a naturally occurring constant region sequence. In one embodiment, the sequence element is disposed in CH3. In one embodiment, one or both of HCP1 and HCP2 were selected to minimize self-dimerization (e.g., HCP1-HCP1) as opposed to heterodimerization (e.g., HCP2-HCP2). In one embodiment, HCP1 and HCP2 are members of a paired protuberance/cavity, e.g., knob and hole pair. In one embodiment, HCP1-HCP2 paring is promoted by an electrostatic interaction. In one embodiment, HCP1-HCP2 paring is promoted

by strand exchange. In one embodiment, HCP1 and HCP2 are not members of a paired protuberance/cavity, e.g., knob and hole pair. In one embodiment, the HCP1 comprises a first heavy chain constant region sequence (HCCRS), wherein the first HCCRS does not comprise a mutation (e.g., a mutation relative to a naturally existing heavy chain constant region sequence). In one embodiment, the HCP2 comprises a second heavy chain constant region sequence (HCCRS), wherein the second HCCRS does not comprise a mutation (e.g., a mutation relative to a naturally existing heavy chain constant region sequence). In one embodiment, i) the HCP1 comprises a first heavy chain constant region sequence (HCCRS), wherein the first HCCRS does not comprise a mutation (e.g., a mutation relative to a naturally existing heavy chain constant region sequence); and ii) the HCP2 comprises a second heavy chain constant region sequence (HCCRS), wherein the second HCCRS does not comprise a mutation (e.g., a mutation relative to a naturally existing heavy chain constant region sequence). In one embodiment, the HCP1 comprises a first CH2 domain sequence and a first CH3 domain sequence, wherein the first CH2 domain sequence and the first CH3 domain sequence do not comprise a mutation (e.g., a mutation relative to a naturally existing CH2 domain sequence or a naturally existing CH3 domain sequence). In one embodiment, the HCP2 comprises a second CH2 domain sequence and a second CH3 domain sequence, wherein the second CH2 domain sequence and the second CH3 domain sequence do not comprise a mutation (e.g., a mutation relative to a naturally existing CH2 domain sequence or a naturally existing CH3 domain sequence). In one embodiment, i) the HCP1 comprises a first CH2 domain sequence and a first CH3 domain sequence, wherein the first CH2 domain sequence and the first CH3 domain sequence do not comprise a mutation (e.g., a mutation relative to a naturally existing CH2 domain sequence or a naturally existing CH3 domain sequence); and ii) the HCP2 comprises a second CH2 domain sequence and a second CH3 domain sequence, wherein the second CH2 domain sequence and the second CH3 domain sequence do not comprise a mutation (e.g., a mutation relative to a naturally existing CH2 domain sequence or a naturally existing CH3 domain sequence).

In certain embodiments of the foregoing aspects, the HCP1 is derived from an antibody arising, either in vivo or in vitro, as a lambda antibody. In certain embodiments of the foregoing aspects, the HCP2 is derived from an antibody arising, either in vivo or in vitro, as a kappa antibody.

In one embodiment, the HCP1 and LLCP comprise amino acid sequences selected from Table 18 (e.g., as paired in Table 18) or Table 5a (e.g., as paired in Table 5a), or functional variant or fragment thereof. In one embodiment, the HCP2 and KLCP comprise amino acid sequences selected from Table 18 (e.g., as paired in Table 18) or Table 5a (e.g., as paired in Table 5a), or functional variant or fragment thereof. In one embodiment, the HCP1, LLCP, HCP2, and KLCP comprise amino acid sequences selected from Table 18 (e.g., a single cell of Table 18) or Table 5a (e.g., a single row of Table 5a), or functional variant or fragment thereof.

In one embodiment, the first or second antigen is a tumor antigen, e.g., a pancreatic, lung, or colorectal tumor antigen. In one embodiment, the first or second antigen is chosen from: PD-L1, HER3, TROP2, mesothelin, IGF-1R, or CA19-9. In one embodiment, the first or second antigen is chosen from: PD-L1, HER3, TROP2, VEGF-A, EGFR, MUC1, DLL4, or HGF. In one embodiment, the first or second antigen is chosen from: PD-L1, HER3, TROP2, VEGF-A, EGFR, MUC1, MAGE-A3, gpA33, NY-ESO-1, ANG2, RSPO3, HER2, CEACAM5, or CEA. In one embodiment, the first or second antigen is an antigen of an immune effector cell, e.g., a T cell, an NK cell, or a myeloid cell. In one embodiment, the first or second antigen is chosen from: CD3, PD-1, LAG-3, TIM-3, CTLA-4, VISTA, TIGIT, PD-L1, B7-H3, 4-1BB, or ICOS. In one embodiment, the first antigen is a tumor antigen, e.g., mesothelin, and the second antigen is an antigen chosen from NKP30, PD-L1, CD3, NKG2D, CD47, 4-1BB, or NKP46; or the second antigen is a tumor antigen, e.g., mesothelin, and the first antigen is an antigen chosen from NKP30, PD-L1, CD3, NKG2D, CD47, 4-1BB, or NKP46. In one embodiment, the first antigen is IGF1R and the second antigen is HER3, or the second antigen is IGF1R and the first antigen is HER3. In one embodiment, the first antigen is mesothelin and the second antigen is PD-L1, or the second antigen is mesothelin and the first antigen is PD-L1. In one embodiment, the first antigen is CTLA4 and the second antigen is IL12β, or the second antigen is CTLA4 and the first antigen is IL12β. In one embodiment, the first antigen is CTLA4 and the second antigen is TRAILR2, or the second antigen is CTLA4 and the first antigen is TRAILR2. In one embodiment, the first antigen is CTLA4 and the second antigen is CD221, or the second antigen is CTLA4 and the first antigen is CD221. In one embodiment, the first antigen is PD1 and the second antigen is TRAILR2, or the second antigen is PD1 and the first antigen is TRAILR2. In one embodiment, the first antigen is PD1 and the second antigen is PDL1, or the second antigen

is PD1 and the first antigen is PDL1. In one embodiment, the first antigen is PD1 and the second antigen is PDL1, or the second antigen is PD1 and the first antigen is PDL1. In one embodiment, the multispecific antibody molecule further comprises an IL-2 molecule. In one embodiment, the multispecific antibody molecule further comprises a CD40 agonist, e.g., a CD40L polypeptide or an agonistic anti-CD40 antibody molecule.

In one aspect, disclosed herein is a multispecific antibody molecule, e.g., an antibody molecule comprising two binding specificities, e.g., a bispecific antibody molecule. The multispecific antibody molecule includes:

a lambda light chain polypeptide (LLCP) specific for a first epitope;

a heavy chain polypeptide 1 (HCP1) specific for the first epitope;

a kappa light chain polypeptide (KLCP) specific for a second epitope; and

a heavy chain polypeptide 2 (HCP2) specific for the second epitope.

In another aspect, disclosed herein is a multispecific, e.g., a bispecific, antibody molecule that includes:

(i) a first heavy chain polypeptide (HCP1) (e.g., a heavy chain polypeptide comprising one, two, three or all of a first heavy chain variable region (first VH), a first CH1, a first heavy chain constant region (e.g., a first CH2, a first CH3, or both)), e.g., wherein the HCP1 binds to a first epitope;

(ii) a second heavy chain polypeptide (HCP2) (e.g., a heavy chain polypeptide comprising one, two, three or all of a second heavy chain variable region (second VH), a second CH1, a second heavy chain constant region (e.g., a second CH2, a second CH3, or both)), e.g., wherein the HCP2 binds to a second epitope;

(iii) a lambda light chain polypeptide (LLCP) (e.g., a lambda light variable region (VLλ), a lambda light constant chain (VLλ), or both) that preferentially associates with the first heavy chain polypeptide (e.g., the first VH), e.g., wherein the LLCP binds to a first epitope; and

(iv) a kappa light chain polypeptide (KLCP) (e.g., a lambda light variable region (VLκ), a lambda light constant chain (VLκ), or both) that preferentially associates with the second heavy chain polypeptide (e.g., the second VH), e.g., wherein the KLCP binds to a second epitope. In

embodiments, the first and second heavy chain polypeptides form an Fc interface that enhances heterodimerization.

In some embodiments of the multispecific antibody molecule disclosed herein:

LLCP has a higher affinity for HCP1 than for HCP2; and/or

KLCP has a higher affinity for HCP2 than for HCP1.

In embodiments, the affinity of LLCP for HCP1 is sufficiently greater than its affinity for HCP2, such that under preselected conditions, e.g., in aqueous buffer, e.g., at pH 7, in saline, e.g., at pH 7, or under physiological conditions, at least 75%, 80, 90, 95, 98, 99, 99.5, or 99.9 % of the multispecific antibody molecule molecules have a LLCPcomplexed, or interfaced with, a HCP1.

In some embodiments of the multispecific antibody molecule disclosed herein:

the HCP1 has a greater affinity for HCP2, than for a second molecule of HCP1; and/or

the HCP2 has a greater affinity for HCP1, than for a second molecule of HCP2.

In embodiments, the affinity of HCP1 for HCP2 is sufficiently greater than its affinity for a second molecule of HCP1, such that under preselected conditions, e.g., in aqueous buffer, e.g., at pH 7, in saline, e.g., at pH 7, or under physiological conditions, at least 75%, 80, 90, 95, 98, 99 99.5 or 99.9 % of the multispecific antibody molecule molecules have a HCP1complexed, or interfaced with, a HCP2.

In another aspect, disclosed herein is a method for making, or producing, a multispecific antibody molecule. The method includes:

(i) providing a first heavy chain polypeptide (e.g., a heavy chain polypeptide comprising one, two, three or all of a first heavy chain variable region (first VH), a first CH1, a first heavy chain constant region (e.g., a first CH2, a first CH3, or both));

(ii) providing a second heavy chain polypeptide (e.g., a heavy chain polypeptide comprising one, two, three or all of a second heavy chain variable region (second VH), a second CH1, a second heavy chain constant region (e.g., a second CH2, a second CH3, or both));

(iii) providing a lambda chain polypeptide (e.g., a lambda light variable region (VLλ), a lambda light constant chain (VLλ), or both) that preferentially associates with the first heavy chain polypeptide (e.g., the first VH); and

(iv) providing a kappa chain polypeptide (e.g., a lambda light variable region (VLκ), a lambda light constant chain (VLκ), or both) that preferentially associates with the second heavy chain polypeptide (e.g., the second VH),

under conditions where (i)-(iv) associate.

In embodiments, the first and second heavy chain polypeptides form an Fc interface that enhances heterodimerization.

In another aspect, disclosed herein is a method for making, or producing, a multispecific antibody molecule. The method includes:

(i) providing a first heavy chain polypeptide (e.g., a heavy chain polypeptide comprising one, two, three or all of a first heavy chain variable region (first VH), a first CH1, a first heavy chain constant region (e.g., a first CH2, a first CH3, or both));

(ii) providing a second heavy chain polypeptide (e.g., a heavy chain polypeptide comprising one, two, three or all of a second heavy chain variable region (second VH), a second CH1, a second heavy chain constant region (e.g., a second CH2, a second CH3, or both));

(iii) providing a lambda chain polypeptide (e.g., a lambda light variable region (VLλ), a lambda light constant chain (VLλ), or both) that preferentially associates with the first heavy chain polypeptide (e.g., the first VH), and further comprising an effector moiety (e.g., IL2); and

(iv) providing a kappa chain polypeptide (e.g., a lambda light variable region (VLκ), a lambda light constant chain (VLλ), or both) that preferentially associates with the second heavy chain polypeptide (e.g., the second VH), and optionally further comprising an antigen binding moiety (e.g., a scFv),

under conditions where (i)-(iv) associate. In embodiments, (i)-(iv) (e.g., nucleic acid encoding (i)-(iv)) are introduced in a single cell, e.g., a single mammalian cell, e.g., a CHO cell. In embodiments, (i)-(iv) are expressed in the cell.

In embodiments, (i)-(iv) (e.g., nucleic acid encoding (i)-(iv)) are introduced in different cells, e.g., different mammalian cells, e.g., two or more CHO cell. In embodiments, (i)-(iv) are expressed in the cells.

In one embodiments, the method further comprises purifying a cell-expressed antibody molecule, e.g., using a lambda- and/or- kappa-specific purification, e.g., affinity chromatography.

In embodiments, the method further comprises evaluating the cell-expressed multispecific antibody molecule. For example, the purified cell-expressed multispecific antibody molecule can be analyzed by techniques known in the art, include mass spectrometry. In one embodiment, the purified cell-expressed antibody molecule is cleaved, e.g., digested with papain to yield the Fab moieties and evaluated using mass spectrometry.

In embodiments, the method produces correctly paired kappa/lambda multispecific, e.g., bispecific, antibody molecules in a high yield, e.g., at least 75%, 80, 90, 95, 98, 99 99.5 or 99.9 %.

Nucleic acid molecules, vectors and host cells encoding the aforesaid multispecific molecules are also disclosed.

Pharmaceutical compositions comprising the aforesaid multispecific molecules and a pharmaceutical acceptable carrier are also disclosed.

In another aspect, the invention features a method of treating a subject having a disorder, e.g., cancer, using the multispecific antibody molecules disclosed herein.

Additional features and embodiments of the multispecific antibody molecules and methods disclosed herein include one or more of the following.

In some embodiments, the multispecific antibody molecule is isolated or purified.

In some embodiments, an interface of a first and second heavy chain polypeptide of the multispecific antibody molecule, e.g., the first and second heavy chain constant regions (e.g., a first and a second Fc region) is altered, e.g., mutated, to increase heterodimerization, e.g., relative to a non-engineered interface, e.g., a naturally-occurring interface. In one embodiment, heterodimerization of the first and second heavy chain polypeptides is enhanced by providing an Fc interface of a first and a second Fc region with one or more of: a paired protuberance-cavity ("knob-in-a hole"), an electrostatic interaction, or a strand-exchange, such that a greater ratio of heteromultimer to homomultimer forms, e.g., relative to a non-engineered interface.In some embodiments, the multispecific antibody molecules include a paired amino acid substitution at a position chosen from one or more of 347, 349, 350, 351, 366, 368, 370, 392, 394, 395, 397, 398, 399, 405, 407, or 409, e.g., of the Fc region of human IgG1 For example, the first immunoglobulin chain constant region (e.g., Fc region) can include a paired an amino acid substitution chosen from: T366S, L368A, or Y407V (e.g., corresponding to a cavity or hole), and

the second immunoglobulin chain constant region comprises a T366W (e.g., corresponding to a protuberance or knob).

In some embodiments, an interface of a first and second heavy chain polypeptide of the multispecific antibody molecule, e.g., the first and second heavy chain constant regions (e.g., a first and a second Fc region) is not altered, e.g., not mutated, to increase heterodimerization, e.g., relative to a non-engineered interface, e.g., a naturally-occurring interface. In one embodiment, heterodimerization of the first and second heavy chain polypeptides is not enhanced by providing an Fc interface of a first and a second Fc region with one or more of: a paired protuberance-cavity ("knob-in-a hole").

In some embodiments, one or more (e.g., all) of a CH1 chain, a lambda light constant chain (VLλ), and a kappa light constant chain (VLκ) is not altered, e.g., not mutated, to increase heterodimerization, e.g., relative to a non-engineered interface, e.g., a naturally-occurring interface. In some embodiments, one or more (e.g., all) of a CH1 chain, a lambda light constant chain (VLλ), and a kappa light constant chain (VLκ) is naturally occurring.

In some embodiments, the heavy chain variable region (VH, e.g., FR1, FR2, FR3, and optionally, CDRs 1-2) is derived from a germline family described by IMGT®, the international ImMunoGeneTics (Lefranc, M.-P., "IMGT, the international ImMunoGeneTics database" *Nucl. Acids Res.*, **29**, 207-209 (2001) and Scaviner, D., Barbié, V., Ruiz, M. and Lefranc, M.-P., "Protein displays of the human immunoglobulin heavy, kappa and lambda variable and joining regions", *Exp. Clin. Immunogenet.*, **16**, 234-240 (1999)), or an amino acid sequence substantially identical thereto.

In some embodiments, the light chain variable region (VL kappa or lambda, e.g., FR1, FR2, FR3, and optionally, CDRs 1-2) is derived from a germline family described by IMGT, or an amino acid sequence substantially identical thereto.

In embodiments, the multispecific antibody molecules include a plurality (e.g., two, three or more) binding specificities (or functionalities).

In an embodiment, the multispecific antibody molecule is a bispecific (or bifunctional) molecule, a trispecific (or trifunctional) molecule, or a tetraspecific (or tetrafunctional) molecule.

In some embodiments, the multispecific antibody molecules include a first binding specificity to a first epitope, and a second binding specificity to a second epitope. In some embodiments, the first and second epitopes are on the same antigen, e.g., the same polypeptide. In other embodiments, the first and second epitopes are on different antigens, e.g., different polypeptide. In some embodiments, the first epitope is on a first antigen, e.g., a first polypeptide and the second epitope is on a second antigen, e.g., a second polypeptide. In some embodiments, the antigen, or polypeptide, is selected an antigen recognized by an antibody from **Tables 2, 4, 5a, 17** and **18**, e.g., a first and second antigen recognized by a lambda and kappa antibody disclosed in **Tables 2, 4, 5a, 17** and **18**. Exemplary pairings of lambda and kappa antibodies are depicted in **Tables 5a** and **18**.

In some embodiments the multispecific antibody molecule includes a first binding specificity to a first epitope, wherein the first epitope is on a tumor antigen, e.g., a pancreatic, lung, or colorectal tumor antigen. In some embodiments, the first epitope is on an antigen chosen from: PD-L1, HER3, TROP2, mesothelin, IGF-1R, or CA19-9. In other embodiments, the first epitope is on an antigen chosen from PD-L1, HER3, TROP2, VEGF-A, EGFR, MUC1, DLL4, or HGF. In yet other embodiments, the first epitope is on an antigen chosen from PD-L1, HER3, TROP2, VEGF-A, EGFR, MUC1, MAGE-A3, gpA33, NY-ESO-1, ANG2, RSPO3, HER2, CEACAM5, or CEA.

In some embodiments, the multispecific antibody molecule includes a second binding specificity to a second epitope, wherein the second epitope is on an antigen of an immune effector cell, e.g., a T cell, an NK cell, or a myeloid cell. In some embodiments, the second epitope is chosen from CD3, PD-1, LAG-3, TIM-3, CTLA-4, VISTA, TIGIT, PD-L1, B7-H3, 4-1BB, or ICOS.

In some embodiments, the multispecific antibody molecule binds to a first epitope on a tumor antigen, e.g., mesothelin, and a second epitope on an antigen chosen from NKP30, PD-L1, CD3, NKG2D, CD47, 4-1BB, or NKP46. In some embodiments, the multispecific antibody molecule binds mesothelin and PD-L1. In some embodiments, the multispecific antibody molecule binds mesothelin andPDL1, and further comprises a cytokine (e.g., IL2). In some embodiments, the multispecific antibody molecule binds mesothelin; PDL1; and NKp30, and further comprises a cytokine (e.g., IL2).

In some embodiments, the multispecific antibody molecules include a plurality (e.g., two or more) binding specificities (or functionalities). In some embodiments, a first binding specificity selectively localizes to a cancer cell, e.g., it includes a tumor- targeting moiety; and the second (or third, or fourth) binding specificity includes one or both of: an immune cell engager (e.g., chosen from one, two, three, or all of an NK cell engager, a B cell engager, a dendritic cell engager, or a macrophage cell engager); and/or a cytokine molecule. Exemplary tumor-targeting moieties, immune cell engagers and cytokine molecules are described in the Detailed Description.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGs. 1A-1D depict a schematic representation of light chain shuffling.

FIG. 2 depicts a schematic representation of a papain-cleaved bispecific antibody showing the location of cleavage in the hinge region by a dotted line. In embodiments, the multispecific antibody molecule having a first binding specificity that includes a hybrid VLλ-CLλ heterodimerized to a first heavy chain variable region-CH1 connected to the Fc constant, CH2-CH3 domain (having a hole modification) and a second binding specificity that includes a hybrid VLκ-CLκ heterodimerized to a second heavy chain variable region-CH1 connected to the Fc constant, CH2-CH3 domain (having a knob modification). Two Fab fragments are released after papain treatment.

FIGs. 3A-3C depict the competition of a lambda light chain polypeptide (LLCP) and a kappa light chain polypeptide (KLCP) for a heavy chain polypeptide (HCP2) when mixed at a 1:1:1

molar ratio utilizing the NanoBiT® Protein:Protein Interaction System (ACS Chem Biol. 2016 Feb 19;**11**(2):400-8.). HCP2 has the LgBiT as a C-terminal fusion, KLCP has the SmBiT as a C-terminal fusion, and LLCP is a native light chain. When HCP2 and KLCP form a Fab region, the LgBiT and SmBiT create a fully functional NanoLuc domain (**FIG. 3A**). When HCP2 and LLCP form a Fab region, the NanoLuc is not complete and is inactive (**FIG. 3B**). A 1:1:1 competition of LLCP and KLCP for HCP2 purified by CH1 affinity results in the HCP2/KLCP functional NanoLuc and the HCP2/LLCP nonfunctional NanoLuc Fab regions (**FIG. 3C**).

FIGs. 4A-4C depict the competition of a lambda light chain polypeptide (LLCP) and a kappa light chain polypeptide (KLCP) for a heavy chain polypeptide (HCP1) when mixed at a 1:1:1 molar ratio utilizing the NanoBiT® Protein:Protein Interaction System. HCP1 has the LgBiT as a C-terminal fusion, LLCP has the SmBiT as a C-terminal fusion, and KLCP is a native light chain. When HCP1 and LLCP form a Fab region, the LgBiT and SmBiT create a fully functional NanoLuc domain (**FIG. 4A**). When HCP1 and KLCP form a Fab region, the NanoLuc is not complete and is inactive (**FIG. 4B**). A 1:1:1 competition of LLCP and KLCP for HCP1 purified by CH1 affinity results in the HCP1/LLCP functional NanoLuc and the HCP1/KLCP nonfunctional NanoLuc Fab regions (**FIG. 4C**).

FIG. 5 depicts a schematic representation of an exemplary multispecific antibody molecule of the present invention. The multispecific antibody molecule comprises a first Fab comprising a kappa light chain polypeptide; a second Fab comprising a lambda light chain polypeptide; and an Fc domain, wherein the Fc domain contains a paired protuberance/cavity, e.g., knob and hole pair. In one embodiment, the first Fab binds to IGF1R and the second Fab binds to HER3 (e.g., multispecific molecule 1 described in Example 2). In one embodiment, the first Fab binds to mesothelin and the second Fab binds to PD-L1 (e.g., multispecific molecule 2 described in Example 3). In one embodiment, the first Fab binds to CTLA-4 and the second Fab binds to IL12β (e.g., multispecific molecule 3 described in Example 4). In one embodiment, the first Fab binds to CTLA-4 and the second Fab binds to TRAILR2 (e.g., multispecific molecule 4 described in Example 5). In one embodiment, the first Fab binds to CTLA-4 and the second Fab binds to CD221 (e.g., multispecific molecule 5 described in Example 6). In one embodiment, the first Fab binds to PD-1 and the second Fab binds to TRAILR2 (e.g., multispecific molecule 6 described in Example 7). In one embodiment, the first Fab binds to PD-1 and the second Fab binds to PDL1 (e.g., multispecific molecule 7 described in Example 8).

FIG. 6 depicts a schematic representation of an exemplary multispecific antibody molecule of the present invention. The multispecific antibody molecule comprises a first Fab comprising a kappa light chain polypeptide; a second Fab comprising a lambda light chain polypeptide; a polypeptide attached to the C terminus of the lambda light chain polypeptide; and an Fc domain, wherein the Fc domain contains a paired protuberance/cavity, e.g., knob and hole pair. In one embodiment, the first Fab binds to CTLA4, the second Fab binds to IL12β, and the polypeptide that is attached to the C terminus of the lambda light chain polypeptide comprises interleukin 2, or fragment or variant thereof (e.g., multispecific molecule 9 described in Example 10).

FIG. 7 depicts a schematic representation of an exemplary multispecific antibody molecule of the present invention. The multispecific antibody molecule comprises a first Fab comprising a kappa light chain polypeptide; a second Fab comprising a lambda light chain polypeptide; a polypeptide attached to the C terminus of the lambda light chain polypeptide; and an Fc domain, wherein the Fc domain does not contain a paired protuberance/cavity, e.g., knob and hole pair (e.g., the Fc domain is a naturally existing Fc domain). In one embodiment, the first Fab binds to CTLA4, the second Fab binds to IL12β, and the polypeptide that is attached to the C terminus of the lambda light chain polypeptide comprises interleukin 2, or fragment or variant thereof (e.g., multispecific molecule 8 described in Example 9).

FIG. 8 depicts a schematic representation of an exemplary multispecific antibody molecule of the present invention. The multispecific antibody molecule comprises a first Fab comprising a kappa light chain polypeptide; a second Fab comprising a lambda light chain polypeptide; a first polypeptide attached to the C terminus of the lambda light chain polypeptide; a second polypeptide attached to the C terminus of the heavy chain polypeptide that associates with the lambda light chain polypeptide; and an Fc domain, wherein the Fc domain contains a paired protuberance/cavity, e.g., knob and hole pair. In one embodiment, the first Fab binds to CTLA4, the second Fab binds to IL12β, the first polypeptide comprises interleukin 2, or fragment or variant thereof, and the second polypeptide comprises interleukin 2, or fragment or variant thereof (e.g., multispecific molecule 11 described in Example 12).

FIG. 9 depicts a schematic representation of an exemplary multispecific antibody molecule of the present invention. The multispecific antibody molecule comprises a first Fab comprising a kappa light chain polypeptide; a second Fab comprising a lambda light chain

polypeptide; a first polypeptide attached to the C terminus of the lambda light chain polypeptide; a second polypeptide attached to the C terminus of the heavy chain polypeptide that associates with the lambda light chain polypeptide; and an Fc domain, wherein the Fc domain does not contain a paired protuberance/cavity, e.g., knob and hole pair (e.g., the Fc domain is a naturally existing Fc domain). In one embodiment, the first Fab binds to CTLA4, the second Fab binds to IL12β, the first polypeptide comprises interleukin 2, or fragment or variant thereof, and the second polypeptide comprises interleukin 2, or fragment or variant thereof (e.g., multispecific molecule 10 described in Example 11).

FIG. 10 depicts a schematic representation of an exemplary multispecific antibody molecule of the present invention. The multispecific antibody molecule comprises a first Fab comprising a kappa light chain polypeptide; a second Fab comprising a lambda light chain polypeptide; a first polypeptide attached to the C terminus of the kappa light chain polypeptide; a second polypeptide attached to the C terminus of the heavy chain polypeptide that associates with the kappa light chain polypeptide; and an Fc domain, wherein the Fc domain contains a paired protuberance/cavity, e.g., knob and hole pair. In one embodiment, the first Fab binds to CTLA4, the second Fab binds to TRAILR2, the first polypeptide comprises interleukin 2, or fragment or variant thereof, and the second polypeptide comprises an scFv (e.g., multispecific molecule 12 described in Example 13).

FIG. 11. Gel of multispecific molecule 1.

FIG. 12. Gel of multispecific molecule 3.

FIG. 13. Gel of multispecific molecule 4.

FIG. 14. Gel of multispecific molecule 5.

FIG. 15. Gel of multispecific molecule 6.

FIG. 16. Gel of multispecific molecule 7.

FIG. 17. Gel of multispecific molecule 8.

FIG. 18. Gel of multispecific molecule 9.

FIG. 19. Size exclusion chromatogram of multispecific molecule 1.

FIG. 20. Size exclusion chromatogram of multispecific molecule 3.

FIG. 21. Size exclusion chromatogram of multispecific molecule 8.

FIG. 22. Size exclusion chromatogram of multispecific molecule 9.

FIG. 23. Gel of reduced samples of multispecific molecule 2 following kappa/lambda select analysis. Lane 1 is the load, lane 2 is the flow-through from the KappaSelect column, lane 3 is the elution from the KappaSelect column, lane 4 is the flow-through from the LambdaFabSelect column, and lane 5 is the elution from the LambdaFabSelect column.

FIG. 24. Gel of reduced samples of multispecific molecule 1 following kappa/lambda select analysis. Lane 1 is the load, lane 2 is the flow-through from the KappaSelect column, lane 3 is the elution from the KappaSelect column, lane 4 is the flow-through from the LambdaFabSelect column, and lane 5 is the elution from the LambdaFabSelect column.

FIG. 25. Gel of reduced samples of multispecific molecule 3 following kappa/lambda select analysis. Lane 1 is the load, lane 2 is the flow-through from the KappaSelect column, lane 3 is the elution from the KappaSelect column, lane 4 is the flow-through from the LambdaFabSelect column, and lane 5 is the elution from the LambdaFabSelect column.

FIG. 26. Gel of reduced samples of multispecific molecule 8 following kappa/lambda select analysis. Lane 1 is the load, lane 2 is the flow-through from the KappaSelect column, lane 3 is the elution from the KappaSelect column, lane 4 is the flow-through from the LambdaFabSelect column, and lane 5 is the elution from the LambdaFabSelect column.

FIG. 27. Gel of reduced samples of multispecific molecule 9 following kappa/lambda select analysis. Lane 1 is the load, lane 2 is the flow-through from the KappaSelect column, lane 3 is the elution from the KappaSelect column, lane 4 is the flow-through from the LambdaFabSelect column, and lane 5 is the elution from the LambdaFabSelect column.

FIG. 28. Gel of reduced samples of multispecific molecule 11 following kappa/lambda select analysis. Lane 1 is the load, lane 2 is the flow-through from the KappaSelect column, lane 3 is the elution from the KappaSelect column, lane 4 is the flow-through from the LambdaFabSelect column, and lane 5 is the elution from the LambdaFabSelect column.

FIG. 29. Gel of reduced samples of multispecific molecule 10 following kappa/lambda select analysis. Lane 1 is the load, lane 2 is the flow-through from the KappaSelect column, lane 3 is the elution from the KappaSelect column, lane 4 is the flow-through from the LambdaFabSelect column, and lane 5 is the elution from the LambdaFabSelect column.

FIG. 30. Gel of reduced samples of multispecific molecule 12 following kappa/lambda select analysis. Lane 1 is the load, lane 2 is the flow-through from the KappaSelect column, lane 3 is the elution from the KappaSelect column, lane 4 is the flow-through from the

LambdaFabSelect column, and lane 5 is the elution from the LambdaFabSelect column. The ratios indicate the DNA ratio used in the transfection from 3:1 to 1:3 of knob to hole.

FIG. 31. Intact mass spectrometry analysis of papain-cleaved multispecific molecule 3.

FIG. 32. Intact mass spectrometry analysis of papain-cleaved multispecific molecule 4.

FIG. 33. Intact mass spectrometry analysis of papain-cleaved multispecific molecule 5.

FIG. 34. Intact mass spectrometry analysis of papain-cleaved multispecific molecule 6.

FIG. 35. Intact mass spectrometry analysis of papain-cleaved multispecific molecule 7.

DETAILED DESCRIPTION OF THE INVENTION

Disclosed herein are multispecific antibody molecules (also referred to herein as "multifunctional antibody molecules") that comprise a lambda light chain polypeptide and a kappa light chain polypeptide. In embodiments, the multispecific antibody molecules include a plurality (e.g., two or more) binding specificities (or functionalities). In some embodiments, a first binding specificity selectively localizes to a cancer cell, e.g., it includes a tumor- targeting moiety; and the second (or third, or fourth) binding specificity includes one or both of: an immune cell engager (e.g., chosen from one, two, three, or all of an NK cell engager, a B cell engager, a dendritic cell engager, or a macrophage cell engager); and/or a cytokine molecule. In an embodiment, the multispecific molecule is a bispecific (or bifunctional) molecule, a trispecific (or trifunctional) molecule, or a tetraspecific (or tetrafunctional) molecule. Accordingly, provided herein are, *inter alia*, multispecific molecules (e.g., multispecific antibody molecules) that include the lambda light chain polypeptide and a kappa light chain polypeptides, nucleic acids encoding the same, methods of producing the aforesaid molecules, and methods of treating a disorder, e.g., cancer, using the aforesaid molecules.

In one embodiment, the multispecific antibody molecule comprises:

(i) a first heavy chain polypeptide (e.g., a heavy chain polypeptide comprising one, two, three or all of a first heavy chain variable region (first VH having a first binding specificity), a first CH1, a first heavy chain constant region (e.g., a first CH2, a first CH3, or both));

(ii) a second heavy chain polypeptide (e.g., a heavy chain polypeptide comprising one, two, three or all of a second heavy chain variable region (second VH), a second CH1, a second heavy chain constant region (e.g., a second CH2, a second CH3, or both));

(iii) a lambda light chain polypeptide (e.g., a lambda light variable region (VLλ), a lambda light constant chain (VLλ), or both) that preferentially associates with the first heavy chain polypeptide (e.g., the first VH); and

(iv) a kappa light chain polypeptide (e.g., a lambda light variable region (VLκ), a lambda light constant chain (VLκ), or both) that preferentially associates with the second heavy chain polypeptide (e.g., the second VH).

In embodiments, the first and second heavy chain polypeptides form an Fc interface that enhances heterodimerization. An exemplary representation is depicted in **FIG. 1A**, which shows a multispecific antibody molecule having a first binding specificity that includes a hybrid VLλ-CLλ heterodimerized to a first heavy chain variable region connected to the Fc constant, CH2-CH3 domain (having a knob modification) and a second binding specificity that includes a hybrid VLκ-CLκ heterodimerized to a second heavy chain variable region connected to the Fc constant, CH2-CH3 domain (having a hole modification).

In some embodiments, disclosed herein is a novel method for generating a multispecific, e.g., a bispecific, antibody molecule. The method for generating bispecific molecules disclosed herein produces stable antibodies, while avoiding the light-chain swapping commonly described in the literature. Light chain swapping or shuffling is a common problem encountered when producing antibodies with a single kappa and a single lambda light chain. A schematic of light chain shuffling is depicted in **FIGs. 1A-1D**. As shown in in **FIGs. 1A-1D**, only 25 % of the product is of the desired configuration (**Fig. 1A**) and the other 75 % of product has the light chains mispaired (**Fig. 1B- 1D**). The method for generating a multispecific, e.g., bispecific, antibody molecule disclosed herein uses antibodies, e.g., human antibodies, with kappa and lambda light chains to produce stable, multispecific, e.g., bispecific, antibody molecules.

Certain terms are defined below.

As used herein, the articles “a” and “an” refer to one or more than one, *e.g.*, to at least one, of the grammatical object of the article. The use of the words "a" or "an" when used in conjunction with the term "comprising" herein may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

As used herein, “about” and “approximately” generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary

degrees of error are within 20 percent (%), typically, within 10%, and more typically, within 5% of a given range of values.

"Antibody molecule" as used herein refers to a protein, e.g., an immunoglobulin chain or fragment thereof, comprising at least one immunoglobulin variable domain sequence. An antibody molecule encompasses antibodies (e.g., full-length antibodies) and antibody fragments. In an embodiment, an antibody molecule comprises an antigen binding or functional fragment of a full length antibody, or a full length immunoglobulin chain. For example, a full-length antibody is an immunoglobulin (Ig) molecule (e.g., an IgG antibody) that is naturally occurring or formed by normal immunoglobulin gene fragment recombinatorial processes). In embodiments, an antibody molecule refers to an immunologically active, antigen-binding portion of an immunoglobulin molecule, such as an antibody fragment. An antibody fragment, e.g., functional fragment, is a portion of an antibody, e.g., Fab, Fab', $F(ab')_2$, $F(ab)_2$, variable fragment (Fv), domain antibody (dAb), or single chain variable fragment (scFv). A functional antibody fragment binds to the same antigen as that recognized by the intact (e.g., full-length) antibody. The terms "antibody fragment" or "functional fragment" also include isolated fragments consisting of the variable regions, such as the "Fv" fragments consisting of the variable regions of the heavy and light chains or recombinant single chain polypeptide molecules in which light and heavy variable regions are connected by a peptide linker ("scFv proteins"). In some embodiments, an antibody fragment does not include portions of antibodies without antigen binding activity, such as Fc fragments or single amino acid residues. Exemplary antibody molecules include full length antibodies and antibody fragments, e.g., dAb (domain antibody), single chain, Fab, Fab', and $F(ab')_2$ fragments, and single chain variable fragments (scFvs).

As used herein, the term "molecule" as used in, e.g., antibody molecule, cytokine molecule, receptor molecule, includes full-length, naturally-occurring molecules, as well as variants, e.g., functional variants (e.g., truncations, fragments, mutated (e.g., substantially similar sequences) or derivatized form thereof), so long as at least one function and/or activity of the unmodified (e.g., naturally-occurring) molecule remains.

The term "functional variant" refers to polypeptides that have a substantially identical amino acid sequence to the naturally-occurring sequence, or are encoded by a substantially identical nucleotide sequence, and are capable of having one or more activities of the naturally-occurring sequence.

"Derived from" as used herein in reference the relationship of a first sequence, to a second sequence (e.g., in the context of nucleic acid sequence or protein sequences) imposes no process limitations and refers only to structural similarity. In embodiments a derived sequence will differ from the reference sequence by levels of homology or sequence identity described elsewhere herein.

As used herein, an "immunoglobulin variable domain sequence" refers to an amino acid sequence which can form the structure of an immunoglobulin variable domain. For example, the sequence may include all or part of the amino acid sequence of a naturally-occurring variable domain. For example, the sequence may or may not include one, two, or more N- or C-terminal amino acids, or may include other alterations that are compatible with formation of the protein structure.

"Lambda light chain polypeptide (LLCP)", as that term is used herein, refers to a polypeptide comprising sufficient light chain (LC) sequence, such that when combined with a cognate heavy chain variable region, can mediate specific binding to its epitope and complex with an HCP1. In an embodiment it comprises all or a fragment of a CH1 region. In an embodiment, an LLCP comprises LC-CDR1, LC-CDR2, LC-CDR3, FR1, FR2, FR3, FR4, and CH1, or sufficient sequence therefrom to mediate specific binding of its epitope and complex with an HCP1. LLCP, together with its HCP1, provide specificity for a first epitope (while KLCP, together with its HCP2, provide specificity for a second epitope). As described elsewhere herein, LLCP has a higher affinity for HCP1 than for HCP2.

"Kappa light chain polypeptide (KLCP)", as that term is used herein, refers to a polypeptide comprising sufficient light chain (LC) sequence, such that when combined with a cognate heavy chain variable region, can mediate specific binding to its epitope and complex with an HCP2. In an embodiment, it comprises all or a fragment of a CH1 region. In an embodiment, a KLCP comprises LC-CDR1, LC-CDR2, LC-CDR3, FR1, FR2, FR3, FR4, and CH1, or sufficient sequence therefrom to mediate specific binding of its epitope and complex with an HCP2. KLCP, together with its HCP2, provide specificity for a second epitope (while LLCP, together with its HCP1, provide specificity for a first epitope).

"Heavy chain polypeptide 1 (HCP1)", as that term is used herein, refers to a polypeptide comprising sufficient heavy chain (HC) sequence, e.g., HC variable region sequence, such that when combined with a cognate LLCP, can mediate specific binding to its epitope and complex

with an HCP1. In an embodiment, it comprises all or a fragment of a CH1region. In an embodiment, it comprises all or a fragment of a CH2 and/or CH3 region. In an embodiment an HCP1 comprises HC-CDR1, HC-CDR2, HC-CDR3, FR1, FR2, FR3, FR4, CH1, CH2, and CH3, or sufficient sequence therefrom to: (i) mediate specific binding of its epitope and complex with an LLCP, (ii) to complex preferentially, as described herein to LLCP as opposed to KLCP; and (iii) to complex preferentially, as described herein, to an HCP2, as opposed to another molecule of HCP1. HCP1, together with its LLCP, provide specificity for a first epitope (while KLCP, together with its HCP2, provide specificity for a second epitope).

"Heavy chain polypeptide 2 (HCP2)", as that term is used herein, refers to a polypeptide comprising sufficient heavy chain (HC) sequence, e.g., HC variable region sequence, such that when combined with a cognate LLCP, can mediate specific binding to its epitope and complex with an HCP1. In an embodiment, it comprises all or a fragment of a CH1region. In an embodiment, it comprises all or a fragment of a CH2 and/or CH3 region. In an embodiment an HCP1 comprises HC-CDR1, HC-CDR2, HC-CDR3, FR1, FR2, FR3, FR4, CH1, CH2, and CH3, or sufficient sequence therefrom to: (i) mediate specific binding of its epitope and complex with an KLCP, (ii) to complex preferentially, as described herein to KLCP as opposed to LLCP; and (iii) to complex preferentially, as described herein, to an HCP1, as opposed to another molecule of HCP2. HCP2, together with its KLCP, provide specificity for a second epitope (while LLCP, together with its HCP1, provide specificity for a first epitope).

In embodiments, an antibody molecule is monospecific, e.g., it comprises binding specificity for a single epitope. In some embodiments, an antibody molecule is multispecific, e.g., it comprises a plurality of immunoglobulin variable domain sequences, where a first immunoglobulin variable domain sequence has binding specificity for a first epitope and a second immunoglobulin variable domain sequence has binding specificity for a second epitope. In some embodiments, an antibody molecule is a bispecific antibody molecule. "Bispecific antibody molecule" as used herein refers to an antibody molecule that has specificity for more than one (e.g., two, three, four, or more) epitope and/or antigen.

"Multispecific antibody molecule" as that term is used herein, refers to an antibody molecule having specificity for two non-identical epitopes, e.g., having a first variable region specific for a first epitope and a second variable region specific for a second epitope, wherein the

first and second epitopes are non-identical. Multispecific antibody molecules include bispecific antibody molecules.

"Antigen" (Ag) as used herein refers to a molecule that can provoke an immune response, e.g., involving activation of certain immune cells and/or antibody generation. Any macromolecule, including almost all proteins or peptides, can be an antigen. Antigens can also be derived from genomic recombinant or DNA. For example, any DNA comprising a nucleotide sequence or a partial nucleotide sequence that encodes a protein capable of eliciting an immune response encodes an "antigen." In embodiments, an antigen does not need to be encoded solely by a full length nucleotide sequence of a gene, nor does an antigen need to be encoded by a gene at all. In embodiments, an antigen can be synthesized or can be derived from a biological sample, e.g., a tissue sample, a tumor sample, a cell, or a fluid with other biological components. As used, herein a "tumor antigen" or interchangeably, a "cancer antigen" includes any molecule present on, or associated with, a cancer, e.g., a cancer cell or a tumor microenvironment that can provoke an immune response. As used, herein an "immune cell antigen" includes any molecule present on, or associated with, an immune cell that can provoke an immune response.

The "antigen-binding site," or "binding portion" of an antibody molecule refers to the part of an antibody molecule, e.g., an immunoglobulin (Ig) molecule, that participates in antigen binding. In embodiments, the antigen binding site is formed by amino acid residues of the variable (V) regions of the heavy (H) and light (L) chains. Three highly divergent stretches within the variable regions of the heavy and light chains, referred to as hypervariable regions, are disposed between more conserved flanking stretches called "framework regions," (FRs). FRs are amino acid sequences that are naturally found between, and adjacent to, hypervariable regions in immunoglobulins. In embodiments, in an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface, which is complementary to the three-dimensional surface of a bound antigen. The three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs." The framework region and CDRs have been defined and described, e.g., in Kabat, E.A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, and Chothia, C. et al. (1987) J. Mol. Biol. 196:901-917. Each variable chain (e.g., variable heavy chain and variable light chain) is

typically made up of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the amino acid order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4.

As used herein, preferential pairing of a heavy chain polypeptide and a light chain polypeptide refers to the condition, where the heavy chain polypeptide and the light chain polypeptide preferentially bind to each other, over an unrelated heavy chain polypeptide, or an unrelated light chain polypeptide. In one embodiment, the heavy chain polypeptide binds to the light chain polypeptide with a higher affinity than when the heavy chain polypeptide binds to an unrelated light chain polypeptide. In one embodiment, the light chain polypeptide binds to the heavy chain polypeptide with a higher affinity than when the light chain polypeptide binds to an unrelated heavy chain polypeptide.

As used here, a percent binding between a first heavy chain polypeptide and a first light chain polypeptide in the presence of a competing polypeptide (e.g., a second heavy chain polypeptide or a second light chain polypeptide) refers to the amount of binding between the first heavy chain polypeptide and the first light chain polypeptide in the presence of the competing polypeptide, relative to the amount of binding between the first heavy chain polypeptide and the first light chain polypeptide in the absence of any competing polypeptide (the latter was set to 100%). In one embodiment, the percent binding was measured when the first heavy chain polypeptide, the first light chain polypeptide, and the competing polypeptide are present at 1:1:1. In one embodiment, the percent binding was measured when the first heavy chain polypeptide, the first light chain polypeptide, and the competing polypeptide are present at 1:1:1, wherein the competing polypeptide is a second light chain polypeptide. In one embodiment, the percent binding was measured by an assay described herein, e.g., the NanoBiT assay.

"Cancer" as used herein can encompass all types of oncogenic processes and/or cancerous growths. In embodiments, cancer includes primary tumors as well as metastatic tissues or malignantly transformed cells, tissues, or organs. In embodiments, cancer encompasses all histopathologies and stages, e.g., stages of invasiveness/severity, of a cancer. In embodiments, cancer includes relapsed and/or resistant cancer. The terms "cancer" and "tumor" can be used interchangeably. For example, both terms encompass solid and liquid tumors. As used herein, the term "cancer" or "tumor" includes premalignant, as well as malignant cancers and tumors.

As used herein, an "immune cell" refers to any of various cells that function in the immune system, e.g., to protect against agents of infection and foreign matter. In embodiments, this term includes leukocytes, e.g., neutrophils, eosinophils, basophils, lymphocytes, and monocytes. Innate leukocytes include phagocytes (e.g., macrophages, neutrophils, and dendritic cells), mast cells, eosinophils, basophils, and natural killer cells. Innate leukocytes identify and eliminate pathogens, either by attacking larger pathogens through contact or by engulfing and then killing microorganisms, and are mediators in the activation of an adaptive immune response. The cells of the adaptive immune system are special types of leukocytes, called lymphocytes. B cells and T cells are important types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow. B cells are involved in the humoral immune response, whereas T cells are involved in cell-mediated immune response. The term "immune cell" includes immune effector cells.

"Immune effector cell," as that term is used herein, refers to a cell that is involved in an immune response, e.g., in the promotion of an immune effector response. Examples of immune effector cells include, but are not limited to, T cells, e.g., alpha/beta T cells and gamma/delta T cells, B cells, natural killer (NK) cells, natural killer T (NK T) cells, and mast cells.

The term "effector function" or "effector response" refers to a specialized function of a cell. Effector function of a T cell, for example, may be cytolytic activity or helper activity including the secretion of cytokines.

In some embodiments, the multispecific antibody molecule includes a tumor-targeting moiety. A "tumor- targeting moiety," as used herein, refers to a binding agent that recognizes or associates with, e.g., binds to, a target in a cancer cell. The tumor- targeting moiety can be an antibody molecule, a receptor molecule (e.g., a full length receptor, receptor fragment, or fusion thereof (e.g., a receptor-Fc fusion)), or a ligand molecule (e.g., a full length ligand, ligand fragment, or fusion thereof (e.g., a ligand-Fc fusion)) that binds to the cancer antigen (e.g., the tumor and/or the stromal antigen). In embodiments, the tumor- targeting moiety specifically binds to the target tumor, e.g., binds preferentially to the target tumor. For example, when the tumor- targeting moiety is an antibody molecule, it binds to the cancer antigen (e.g., the tumor antigen and/or the stromal antigen) with a dissociation constant of less than about 10 nM.

In some embodiments, the multispecific antibody molecule includes an immune cell engager. "An immune cell engager" refers to one or more binding specificities that bind and/or

activate an immune cell, e.g., a cell involved in an immune response. In embodiments, the immune cell is chosen from an NK cell, a B cell, a dendritic cell, and/or the macrophage cell. The immune cell engager can be an antibody molecule, a receptor molecule (e.g., a full length receptor, receptor fragment, or fusion thereof (e.g., a receptor-Fc fusion)), or a ligand molecule (e.g., a full length ligand, ligand fragment, or fusion thereof (e.g., a ligand-Fc fusion)) that binds to the immune cell antigen (e.g., the NK cell antigen, the B cell antigen, the dendritic cell antigen, and/or the macrophage cell antigen). In embodiments, the immune cell engager specifically binds to the target immune cell, e.g., binds preferentially to the target immune cell. For example, when the immune cell engager is an antibody molecule, it binds to the immune cell antigen (e.g., the NK cell antigen, the B cell antigen, the dendritic cell antigen, and/or the macrophage cell antigen) with a dissociation constant of less than about 10 nM.

In some embodiments, the multispecific antibody molecule includes a cytokine molecule. As used herein, a "cytokine molecule" refers to full length, a fragment or a variant of a cytokine; a cytokine further comprising a receptor domain, e.g., a cytokine receptor dimerizing domain; or an agonist of a cytokine receptor, e.g., an antibody molecule (e.g., an agonistic antibody) to a cytokine receptor, that elicits at least one activity of a naturally-occurring cytokine. In some embodiments the cytokine molecule is chosen from interleukin-2 (IL-2), interleukin-12 (IL-12), interleukin-15 (IL-15), interleukin-18 (IL-18), interleukin-21 (IL-21), or interferon gamma, or a fragment or variant thereof, or a combination of any of the aforesaid cytokines. The cytokine molecule can be a monomer or a dimer. In embodiments, the cytokine molecule can further include a cytokine receptor dimerizing domain. In other embodiments, the cytokine molecule is an agonist of a cytokine receptor, e.g., an antibody molecule (e.g., an agonistic antibody) to a cytokine receptor chosen from an IL-2, IL-15Ra or IL-21R.

The compositions and methods of the present invention encompass polypeptides and nucleic acids having the sequences specified, or sequences substantially identical or similar thereto, *e.g.*, sequences at least 85%, 90%, 95% identical or higher to the sequence specified. In the context of an amino acid sequence, the term "substantially identical" is used herein to refer to a first amino acid that contains a sufficient or minimum number of amino acid residues that are i) identical to, or ii) conservative substitutions of aligned amino acid residues in a second amino acid sequence such that the first and second amino acid sequences can have a common structural domain and/or common functional activity. For example, amino acid sequences that contain a

common structural domain having at least about 85%, 90%. 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to a reference sequence, *e.g.*, a sequence provided herein.

In the context of nucleotide sequence, the term "substantially identical" is used herein to refer to a first nucleic acid sequence that contains a sufficient or minimum number of nucleotides that are identical to aligned nucleotides in a second nucleic acid sequence such that the first and second nucleotide sequences encode a polypeptide having common functional activity, or encode a common structural polypeptide domain or a common functional polypeptide activity. For example, nucleotide sequences having at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to a reference sequence, *e.g.*, a sequence provided herein.

Calculations of homology or sequence identity between sequences (the terms are used interchangeably herein) are performed as follows.

To determine the percent identity of two amino acid sequences, or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, 60%, and even more preferably at least 70%, 80%, 90%, 100% of the length of the reference sequence. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology").

The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch ((1970) *J. Mol. Biol.* 48:444-453) algorithm which has been incorporated into the GAP program in the GCG software package (available at http://www.gcg.com), using either a

Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available at http://www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. A particularly preferred set of parameters (and the one that should be used unless otherwise specified) are a Blossum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5.

The percent identity between two amino acid or nucleotide sequences can be determined using the algorithm of E. Meyers and W. Miller ((1989) *CABIOS*, 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences described herein can be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid (e.g., SEQ ID NO: 1) molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See http://www.ncbi.nlm.nih.gov.

It is understood that the molecules of the present invention may have additional conservative or non-essential amino acid substitutions, which do not have a substantial effect on their functions.

The term "amino acid" is intended to embrace all molecules, whether natural or synthetic, which include both an amino functionality and an acid functionality and capable of being included in a polymer of naturally-occurring amino acids. Exemplary amino acids include naturally-occurring amino acids; analogs, derivatives and congeners thereof; amino acid analogs

having variant side chains; and all stereoisomers of any of any of the foregoing. As used herein the term "amino acid" includes both the D- or L- optical isomers and peptidomimetics.

A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.,* alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine).

The terms "polypeptide", "peptide" and "protein" (if single chain) are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation, such as conjugation with a labeling component. The polypeptide can be isolated from natural sources, can be a produced by recombinant techniques from a eukaryotic or prokaryotic host, or can be a product of synthetic procedures.

The terms "nucleic acid," "nucleic acid sequence," "nucleotide sequence," or "polynucleotide sequence," and "polynucleotide" are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. The polynucleotide may be either single-stranded or double-stranded, and if single-stranded may be the coding strand or non-coding (antisense) strand. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. The nucleic acid may be a recombinant polynucleotide, or a polynucleotide of genomic, cDNA, semisynthetic, or synthetic origin which either does not occur in nature or is linked to another polynucleotide in a non-natural arrangement.

The term "isolated," as used herein, refers to material that is removed from its original or native environment (*e.g.*, the natural environment if it is naturally occurring). For example, a

naturally-occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or polypeptide, separated by human intervention from some or all of the co-existing materials in the natural system, is isolated. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition, and still be isolated in that such vector or composition is not part of the environment in which it is found in nature.

Various aspects of the invention are described in further detail below. Additional definitions are set out throughout the specification.

Antibody Molecules

In one embodiment, the antibody molecule binds to an antigen, e.g., an immune effector cell, a tumor antigen or a stromal antigen. In some embodiments, the antigen is, *e.g.*, a mammalian, e.g., a human, antigen. In other embodiments, the antibody molecule binds to an immune cell antigen, *e.g.*, a mammalian, e.g., a human, immune cell antigen. For example, the antibody molecule binds specifically to an epitope, *e.g.*, linear or conformational epitope, on the cancer antigen or the immune cell antigen.

In an embodiment, an antibody molecule is a monospecific antibody molecule and binds a single epitope. *E.g.*, a monospecific antibody molecule having a plurality of immunoglobulin variable domain sequences, each of which binds the same epitope.

In an embodiment an antibody molecule is a multispecific antibody molecule, *e.g.*, it comprises a plurality of immunoglobulin variable domains sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In an embodiment the first and second epitopes are on the same antigen, *e.g.*, the same protein (or subunit of a multimeric protein). In an embodiment the first and second epitopes overlap. In an embodiment the first and second epitopes do not overlap. In an embodiment the first and second epitopes are on different antigens, *e.g.*, the different proteins (or different subunits of a multimeric protein). In an embodiment a multispecific antibody molecule comprises a third, fourth or fifth immunoglobulin variable domain. In an embodiment, a multispecific antibody molecule is a bispecific antibody molecule, a trispecific antibody molecule, or a tetraspecific antibody molecule.

In an embodiment a multispecific antibody molecule is a bispecific antibody molecule. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody molecule is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. In an embodiment the first and second epitopes are on the same antigen, *e.g.*, the same protein (or subunit of a multimeric protein). In an embodiment the first and second epitopes overlap. In an embodiment the first and second epitopes do not overlap. In an embodiment the first and second epitopes are on different antigens, *e.g.*, the different proteins (or different subunits of a multimeric protein). In an embodiment a bispecific antibody molecule comprises a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a first epitope and a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a half antibody having binding specificity for a first epitope and a half antibody having binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a half antibody, or fragment thereof, having binding specificity for a first epitope and a half antibody, or fragment thereof, having binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a scFv or a Fab, or fragment thereof, have binding specificity for a first epitope and a scFv or a Fab, or fragment thereof, have binding specificity for a second epitope.

In an embodiment, an antibody molecule comprises a diabody, and a single-chain molecule, as well as an antigen-binding fragment of an antibody (*e.g.,* Fab, F(ab')$_2$, and Fv). For example, an antibody molecule can include a heavy (H) chain variable domain sequence (abbreviated herein as VH), and a light (L) chain variable domain sequence (abbreviated herein as VL). In an embodiment an antibody molecule comprises or consists of a heavy chain and a light chain (referred to herein as a half antibody. In another example, an antibody molecule includes two heavy (H) chain variable domain sequences and two light (L) chain variable domain sequence, thereby forming two antigen binding sites, such as Fab, Fab', F(ab')$_2$, Fc, Fd, Fd', Fv, single chain antibodies (scFv for example), single variable domain antibodies, diabodies (Dab) (bivalent and bispecific), and chimeric (*e.g.*, humanized) antibodies, which may be produced by the modification of whole antibodies or those synthesized de novo using recombinant DNA

technologies. These functional antibody fragments retain the ability to selectively bind with their respective antigen or receptor. Antibodies and antibody fragments can be from any class of antibodies including, but not limited to, IgG, IgA, IgM, IgD, and IgE, and from any subclass (*e.g.*, IgG1, IgG2, IgG3, and IgG4) of antibodies. The a preparation of antibody molecules can be monoclonal or polyclonal. An antibody molecule can also be a human, humanized, CDR-grafted, or *in vitro* generated antibody. The antibody can have a heavy chain constant region chosen from, *e.g.*, IgG1, IgG2, IgG3, or IgG4. The antibody can also have a light chain chosen from, *e.g.*, kappa or lambda. The term "immunoglobulin" (Ig) is used interchangeably with the term "antibody" herein.

Examples of antigen-binding fragments of an antibody molecule include: (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a diabody (dAb) fragment, which consists of a VH domain; (vi) a camelid or camelized variable domain; (vii) a single chain Fv (scFv), *see e.g.*, Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883); (viii) a single domain antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

Antibody molecules include intact molecules as well as functional fragments thereof. Constant regions of the antibody molecules can be altered, *e.g.*, mutated, to modify the properties of the antibody (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function).

Antibody molecules can also be single domain antibodies. Single domain antibodies can include antibodies whose complementary determining regions are part of a single domain polypeptide. Examples include, but are not limited to, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies and single domain scaffolds other than those derived from antibodies. Single domain antibodies may be any of the art, or any future single domain antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, fish, shark, goat, rabbit, and bovine. According to another

aspect of the invention, a single domain antibody is a naturally occurring single domain antibody known as heavy chain antibody devoid of light chains. Such single domain antibodies are disclosed in WO 9404678, for example. For clarity reasons, this variable domain derived from a heavy chain antibody naturally devoid of light chain is known herein as a VHH or nanobody to distinguish it from the conventional VH of four chain immunoglobulins. Such a VHH molecule can be derived from antibodies raised in *Camelidae* species, for example in camel, llama, dromedary, alpaca and guanaco. Other species besides *Camelidae* may produce heavy chain antibodies naturally devoid of light chain; such VHHs are within the scope of the invention.

The VH and VL regions can be subdivided into regions of hypervariability, termed "complementarity determining regions" (CDR), interspersed with regions that are more conserved, termed "framework regions" (FR or FW).

The extent of the framework region and CDRs has been precisely defined by a number of methods (*see*, Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Chothia, C. *et al.* (1987) *J. Mol. Biol.* 196:901-917; and the AbM definition used by Oxford Molecular's AbM antibody modeling software. *See*, generally, *e.g.*, *Protein Sequence and Structure Analysis of Antibody Variable Domains.* In: Antibody Engineering Lab Manual (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg).

The terms “complementarity determining region,” and “CDR,” as used herein refer to the sequences of amino acids within antibody variable regions which confer antigen specificity and binding affinity. In general, there are three CDRs in each heavy chain variable region (HCDR1, HCDR2, HCDR3) and three CDRs in each light chain variable region (LCDR1, LCDR2, LCDR3).

The precise amino acid sequence boundaries of a given CDR can be determined using any of a number of known schemes, including those described by Kabat *et al.* (1991), “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (“Kabat” numbering scheme), Al-Lazikani *et al.*, (1997) *JMB* 273,927-948 (“Chothia” numbering scheme). As used herein, the CDRs defined according the “Chothia” number scheme are also sometimes referred to as “hypervariable loops.”

For example, under Kabat, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3); and the

CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3). Under Chothia, the CDR amino acids in the VH are numbered 26-32 (HCDR1), 52-56 (HCDR2), and 95-102 (HCDR3); and the amino acid residues in VL are numbered 26-32 (LCDR1), 50-52 (LCDR2), and 91-96 (LCDR3).

Each VH and VL typically includes three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

The antibody molecule can be a polyclonal or a monoclonal antibody.

The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. A monoclonal antibody can be made by hybridoma technology or by methods that do not use hybridoma technology (*e.g.*, recombinant methods).

The antibody can be recombinantly produced, *e.g.,* produced by phage display or by combinatorial methods.

Phage display and combinatorial methods for generating antibodies are known in the art (as described in, *e.g.,* Ladner *et al.* U.S. Patent No. 5,223,409; Kang *et al.* International Publication No. WO 92/18619; Dower *et al.* International Publication No. WO 91/17271; Winter *et al.* International Publication WO 92/20791; Markland *et al.* International Publication No. WO 92/15679; Breitling *et al.* International Publication WO 93/01288; McCafferty *et al.* International Publication No. WO 92/01047; Garrard *et al.* International Publication No. WO 92/09690; Ladner *et al.* International Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum Antibod Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J Mol Biol* 226:889-896; Clackson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *PNAS* 89:3576-3580; Garrad *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc Acid Res* 19:4133-4137; and Barbas *et al.* (1991) *PNAS* 88:7978-7982, the contents of all of which are incorporated by reference herein).

In one embodiment, the antibody is a fully human antibody (*e.g.*, an antibody made in a mouse which has been genetically engineered to produce an antibody from a human immunoglobulin sequence), or a non-human antibody, *e.g.,* a rodent (mouse or rat), goat, primate

(*e.g.*, monkey), camel antibody. Preferably, the non-human antibody is a rodent (mouse or rat antibody). Methods of producing rodent antibodies are known in the art.

Human monoclonal antibodies can be generated using transgenic mice carrying the human immunoglobulin genes rather than the mouse system. Splenocytes from these transgenic mice immunized with the antigen of interest are used to produce hybridomas that secrete human mAbs with specific affinities for epitopes from a human protein (see, *e.g.*, Wood *et al.* International Application WO 91/00906, Kucherlapati *et al.* PCT publication WO 91/10741; Lonberg *et al.* International Application WO 92/03918; Kay *et al.* International Application 92/03917; Lonberg, N. *et al.* 1994 *Nature* 368:856-859; Green, L.L. *et al.* 1994 *Nature Genet.* 7:13-21; Morrison, S.L. *et al.* 1994 *Proc. Natl. Acad. Sci. USA* 81:6851-6855; Bruggeman *et al.* 1993 *Year Immunol* 7:33-40; Tuaillon *et al.* 1993 *PNAS* 90:3720-3724; Bruggeman *et al.* 1991 *Eur J Immunol* 21:1323-1326).

An antibody molecule can be one in which the variable region, or a portion thereof, *e.g.*, the CDRs, are generated in a non-human organism, *e.g.*, a rat or mouse. Chimeric, CDR-grafted, and humanized antibodies are within the invention. Antibody molecules generated in a non-human organism, *e.g.*, a rat or mouse, and then modified, *e.g.*, in the variable framework or constant region, to decrease antigenicity in a human are within the invention.

An "effectively human" protein is a protein that does substantially not evoke a neutralizing antibody response, *e.g.*, the human anti-murine antibody (HAMA) response. HAMA can be problematic in a number of circumstances, *e.g.*, if the antibody molecule is administered repeatedly, *e.g.*, in treatment of a chronic or recurrent disease condition. A HAMA response can make repeated antibody administration potentially ineffective because of an increased antibody clearance from the serum (*see, e.g.,* Saleh *et al.*, *Cancer Immunol. Immunother.*, 32:180-190 (1990)) and also because of potential allergic reactions (*see, e.g.,* LoBuglio *et al., Hybridoma*, 5:5117-5123 (1986)).

Chimeric antibodies can be produced by recombinant DNA techniques known in the art (see Robinson *et al.*, International Patent Publication PCT/US86/02269; Akira, *et al.,* European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison *et al.,* European Patent Application 173,494; Neuberger *et al.*, International Application WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567; Cabilly *et al.*, European Patent Application 125,023; Better *et al.* (1988 *Science* 240:1041-1043); Liu *et al.* (1987) *PNAS* 84:3439-3443; Liu

et al., 1987, *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *PNAS* 84:214-218; Nishimura *et al.*, 1987, *Canc. Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; and Shaw *et al.*, 1988, *J. Natl Cancer Inst.* 80:1553-1559).

A humanized or CDR-grafted antibody will have at least one or two but generally all three recipient CDRs (of heavy and or light immuoglobulin chains) replaced with a donor CDR. The antibody may be replaced with at least a portion of a non-human CDR or only some of the CDRs may be replaced with non-human CDRs. It is only necessary to replace the number of CDRs required for binding to the antigen. Preferably, the donor will be a rodent antibody, *e.g.,* a rat or mouse antibody, and the recipient will be a human framework or a human consensus framework. Typically, the immunoglobulin providing the CDRs is called the "donor" and the immunoglobulin providing the framework is called the "acceptor." In one embodiment, the donor immunoglobulin is a non-human (*e.g.,* rodent). The acceptor framework is a naturally-occurring (*e.g.,* a human) framework or a consensus framework, or a sequence about 85% or higher, preferably 90%, 95%, 99% or higher identical thereto.

As used herein, the term "consensus sequence" refers to the sequence formed from the most frequently occurring amino acids (or nucleotides) in a family of related sequences (See *e.g.*, Winnaker, From Genes to Clones (Verlagsgesellschaft, Weinheim, Germany 1987). In a family of proteins, each position in the consensus sequence is occupied by the amino acid occurring most frequently at that position in the family. If two amino acids occur equally frequently, either can be included in the consensus sequence. A "consensus framework" refers to the framework region in the consensus immunoglobulin sequence.

An antibody molecule can be humanized by methods known in the art (*see e.g.,* Morrison, S. L., 1985, *Science* 229:1202-1207, by Oi *et al.,* 1986, *BioTechniques* 4:214, and by Queen *et al.* US 5,585,089, US 5,693,761 and US 5,693,762, the contents of all of which are hereby incorporated by reference).

Humanized or CDR-grafted antibody molecules can be produced by CDR-grafting or CDR substitution, wherein one, two, or all CDRs of an immunoglobulin chain can be replaced. *See e.g.*, U.S. Patent 5,225,539; Jones *et al.* 1986 *Nature* 321:552-525; Verhoeyan *et al.* 1988 *Science* 239:1534; Beidler *et al.* 1988 *J. Immunol.* 141:4053-4060; Winter US 5,225,539, the contents of all of which are hereby expressly incorporated by reference. Winter describes a CDR-grafting method which may be used to prepare the humanized antibodies of the present

invention (UK Patent Application GB 2188638A, filed on March 26, 1987; Winter US 5,225,539), the contents of which is expressly incorporated by reference.

Also within the scope of the invention are humanized antibody molecules in which specific amino acids have been substituted, deleted or added. Criteria for selecting amino acids from the donor are described in US 5,585,089, *e.g.*, columns 12-16 of US 5,585,089, *e.g.*, columns 12-16 of US 5,585,089, the contents of which are hereby incorporated by reference. Other techniques for humanizing antibodies are described in Padlan *et al.* EP 519596 A1, published on December 23, 1992.

The antibody molecule can be a single chain antibody. A single-chain antibody (scFV) may be engineered (see, for example, Colcher, D. *et al.* (1999) *Ann N Y Acad Sci* 880:263-80; and Reiter, Y. (1996) *Clin Cancer Res* 2:245-52). The single chain antibody can be dimerized or multimerized to generate multivalent antibodies having specificities for different epitopes of the same target protein.

In yet other embodiments, the antibody molecule has a heavy chain constant region chosen from, *e.g.*, the heavy chain constant regions of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE; particularly, chosen from, *e.g.*, the (*e.g.*, human) heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4. In another embodiment, the antibody molecule has a light chain constant region chosen from, *e.*g., the (*e.g.*, human) light chain constant regions of kappa or lambda. The constant region can be altered, *e.g.*, mutated, to modify the properties of the antibody (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, and/or complement function). In one embodiment the antibody has: effector function; and can fix complement. In other embodiments the antibody does not; recruit effector cells; or fix complement. In another embodiment, the antibody has reduced or no ability to bind an Fc receptor. For example, it is a isotype or subtype, fragment or other mutant, which does not support binding to an Fc receptor, *e.g.*, it has a mutagenized or deleted Fc receptor binding region.

Methods for altering an antibody constant region are known in the art. Antibodies with altered function, *e.g.* altered affinity for an effector ligand, such as FcR on a cell, or the C1 component of complement can be produced by replacing at least one amino acid residue in the constant portion of the antibody with a different residue (*see e.g.,* EP 388,151 A1, U.S. Pat. No. 5,624,821 and U.S. Pat. No. 5,648,260, the contents of all of which are hereby incorporated by

reference). Similar type of alterations could be described which if applied to the murine, or other species immunoglobulin would reduce or eliminate these functions.

An antibody molecule can be derivatized or linked to another functional molecule (*e.g.*, another peptide or protein). As used herein, a "derivatized" antibody molecule is one that has been modified. Methods of derivatization include but are not limited to the addition of a fluorescent moiety, a radionucleotide, a toxin, an enzyme or an affinity ligand such as biotin. Accordingly, the antibody molecules of the invention are intended to include derivatized and otherwise modified forms of the antibodies described herein, including immunoadhesion molecules. For example, an antibody molecule can be functionally linked (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (*e.g.*, a bispecific antibody or a diabody), a detectable agent, a cytotoxic agent, a pharmaceutical agent, and/or a protein or peptide that can mediate association of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag).

One type of derivatized antibody molecule is produced by crosslinking two or more antibodies (of the same type or of different types, *e.g.,* to create bispecific antibodies). Suitable crosslinkers include those that are heterobifunctional, having two distinctly reactive groups separated by an appropriate spacer (*e.g.*, m-maleimidobenzoyl-N-hydroxysuccinimide ester) or homobifunctional (*e.g.*, disuccinimidyl suberate). Such linkers are available from Pierce Chemical Company, Rockford, Ill.

Multispecific antibody molecules

In embodiments, multispecific antibody molecules can comprise more than one antigen-binding site, where different sites are specific for different antigens. In embodiments, multispecific antibody molecules can bind more than one (e.g., two or more) epitopes on the same antigen. In embodiments, multispecific antibody molecules comprise an antigen-binding site specific for a target cell (e.g., cancer cell) and a different antigen-binding site specific for an immune effector cell. In one embodiment, the multispecific antibody molecule is a bispecific antibody molecule. Bispecific antibody molecules can be classified into five different structural groups: (i) bispecific immunoglobulin G (BsIgG); (ii) IgG appended with an additional antigen-

binding moiety; (iii) bispecific antibody fragments; (iv) bispecific fusion proteins; and (v) bispecific antibody conjugates.

BsIgG is a format that is monovalent for each antigen. Exemplary BsIgG formats include but are not limited to crossMab, DAF (two-in-one), DAF (four-in-one), DutaMab, DT-IgG, knobs-in-holes common LC, knobs-in-holes assembly, charge pair, Fab-arm exchange, SEEDbody, triomab, LUZ-Y, Fcab, κλ-body, orthogonal Fab. *See* Spiess et al. Mol. Immunol. 67(2015):95-106. Exemplary BsIgGs include catumaxomab (Fresenius Biotech, Trion Pharma, Neopharm), which contains an anti-CD3 arm and an anti-EpCAM arm; and ertumaxomab (Neovii Biotech, Fresenius Biotech), which targets CD3 and HER2. In some embodiments, BsIgG comprises heavy chains that are engineered for heterodimerization. For example, heavy chains can be engineered for heterodimerization using a "knobs-into-holes" strategy, a SEED platform, a common heavy chain (e.g., in κλ-bodies), and use of heterodimeric Fc regions. *See* Spiess et al. Mol. Immunol. 67(2015):95-106. Strategies that have been used to avoid heavy chain pairing of homodimers in BsIgG include knobs-in-holes, duobody, azymetric, charge pair, HA-TF, SEEDbody, and differential protein A affinity. *See Id.*

BsIgG can be produced by separate expression of the component antibodies in different host cells and subsequent purification/assembly into a BsIgG. BsIgG can also be produced by expression of the component antibodies in a single host cell. BsIgG can be purified using affinity chromatography, e.g., using protein A and sequential pH elution.

IgG appended with an additional antigen-binding moiety is another format of bispecific antibody molecules. For example, monospecific IgG can be engineered to have bispecificity by appending an additional antigen-binding unit onto the monospecific IgG, e.g., at the N- or C-terminus of either the heavy or light chain. Exemplary additional antigen-binding units include single domain antibodies (e.g., variable heavy chain or variable light chain), engineered protein scaffolds, and paired antibody variable domains (e.g., single chain variable fragments or variable fragments). *See Id.* Examples of appended IgG formats include dual variable domain IgG (DVD-Ig), IgG(H)-scFv, scFv-(H)IgG, IgG(L)-scFv, scFv-(L)IgG, IgG(L,H)-Fv, IgG(H)-V, V(H)-IgG, IgG(L)-V, V(L)-IgG, KIH IgG-scFab, 2scFv-IgG, IgG-2scFv, scFv4-Ig, zybody, and DVI-IgG (four-in-one). *See* Spiess et al. Mol. Immunol. 67(2015):95-106. An example of an IgG-scFv is MM-141 (Merrimack Pharmaceuticals), which binds IGF-1R and HER3. Examples

of DVD-Ig include ABT-981 (AbbVie), which binds IL-1α and IL-1β; and ABT-122 (AbbVie), which binds TNF and IL-17A.

Bispecific antibody fragments (BsAb) are a format of bispecific antibody molecules that lack some or all of the antibody constant domains. For example, some BsAb lack an Fc region. In embodiments, bispecific antibody fragments include heavy and light chain regions that are connected by a peptide linker that permits efficient expression of the BsAb in a single host cell. Exemplary bispecific antibody fragments include but are not limited to nanobody, nanobody-HAS, BiTE, Diabody, DART, TandAb, scDiabody, scDiabody-CH3, Diabody-CH3, triple body, miniantibody, minibody, TriBi minibody, scFv-CH3 KIH, Fab-scFv, scFv-CH-CL-scFv, F(ab')2, F(ab')2-scFv2, scFv-KIH, Fab-scFv-Fc, tetravalent HCAb, scDiabody-Fc, Diabody-Fc, tandem scFv-Fc, and intrabody. *See Id.* For example, the BiTE format comprises tandem scFvs, where the component scFvs bind to CD3 on T cells and a surface antigen on cancer cells

Bispecific fusion proteins include antibody fragments linked to other proteins, e.g., to add additional specificity and/or functionality. An example of a bispecific fusion protein is an immTAC, which comprises an anti-CD3 scFv linked to an affinity-matured T-cell receptor that recognizes HLA-presented peptides. In embodiments, the dock-and-lock (DNL) method can be used to generate bispecific antibody molecules with higher valency. Also, fusions to albumin binding proteins or human serum albumin can be extend the serum half-life of antibody fragments. *See Id.*

CDR-grafted scaffolds

In embodiments, the antibody molecule is a CDR-grafted scaffold domain. In embodiments, the scaffold domain is based on a fibronectin domain, e.g., fibronectin type III domain. The overall fold of the fibronectin type III (Fn3) domain is closely related to that of the smallest functional antibody fragment, the variable domain of the antibody heavy chain. There are three loops at the end of Fn3; the positions of BC, DE and FG loops approximately correspond to those of CDR1, 2 and 3 of the VH domain of an antibody. Fn3 does not have disulfide bonds; and therefore Fn3 is stable under reducing conditions, unlike antibodies and their fragments (see, e.g., WO 98/56915; WO 01/64942; WO 00/34784). An Fn3 domain can be modified (e.g., using CDRs or hypervariable loops described herein) or varied, e.g., to select domains that bind to an antigen/marker/cell described herein.

In embodiments, a scaffold domain, e.g., a folded domain, is based on an antibody, e.g., a "minibody" scaffold created by deleting three beta strands from a heavy chain variable domain of a monoclonal antibody (see, e.g., Tramontano et al., 1994, J Mol. Recognit. 7:9; and Martin et al., 1994, EMBO J. 13:5303-5309). The "minibody" can be used to present two hypervariable loops. In embodiments, the scaffold domain is a V-like domain (see, e.g., Coia et al. WO 99/45110) or a domain derived from tendamistatin, which is a 74 residue, six-strand beta sheet sandwich held together by two disulfide bonds (see, e.g., McConnell and Hoess, 1995, J Mol. Biol. 250:460). For example, the loops of tendamistatin can be modified (e.g., using CDRs or hypervariable loops) or varied, e.g., to select domains that bind to a marker/antigen/cell described herein. Another exemplary scaffold domain is a beta-sandwich structure derived from the extracellular domain of CTLA-4 (see, e.g., WO 00/60070).

Other exemplary scaffold domains include but are not limited to T-cell receptors; MHC proteins; extracellular domains (e.g., fibronectin Type III repeats, EGF repeats); protease inhibitors (e.g., Kunitz domains, ecotin, BPTI, and so forth); TPR repeats; trifoil structures; zinc finger domains; DNA-binding proteins; particularly monomeric DNA binding proteins; RNA binding proteins; enzymes, e.g., proteases (particularly inactivated proteases), RNase; chaperones, e.g., thioredoxin, and heat shock proteins; and intracellular signaling domains (such as SH2 and SH3 domains). See, e.g., US 20040009530 and US 7,501,121, incorporated herein by reference.

In embodiments, a scaffold domain is evaluated and chosen, e.g., by one or more of the following criteria: (1) amino acid sequence, (2) sequences of several homologous domains, (3) 3-dimensional structure, and/or (4) stability data over a range of pH, temperature, salinity, organic solvent, oxidant concentration. In embodiments, the scaffold domain is a small, stable protein domain, e.g., a protein of less than 100, 70, 50, 40 or 30 amino acids. The domain may include one or more disulfide bonds or may chelate a metal, e.g., zinc.

Exemplary structures of the multifunctional molecules defined herein are described below. Exemplary structures are further described in: Weidle U et al. (2013) The Intriguing Options of Multispecific Antibody Formats for Treatment of Cancer. *Cancer Genomics & Proteomics* 10: 1-18 (2013); and Spiess C et al. (2015) Alternative molecular formats and therapeutic applications for bispecific antibodies. *Molecular Immunology* 67: 95-106; the full contents of each of which is incorporated by reference herein).

Heterodimerized Antibody Molecules

Heterodimerized bispecific antibodies are based on the natural IgG structure, wherein the two binding arms recognize different antigens. IgG derived formats that enable defined monovalent (and simultaneous) antigen binding are generated by forced heavy chain heterodimerization, combined with technologies that minimize light chain mispairing (e.g., common light chain). Forced heavy chain heterodimerization can be obtained using, e.g., knob-in-hole OR strand exchange engineered domains (SEED).

Knob-in-Hole

Knob-in-Hole as described in US 5,731,116, US 7,476,724 and Ridgway, J. *et al.* (1996) *Prot. Engineering* 9(7): 617-621, broadly involves: *(1)* mutating the CH3 domain of one or both antibodies to promote heterodimerization; and (2) combining the mutated antibodies under conditions that promote heterodimerization. "Knobs" or "protuberances" are typically created by replacing a small amino acid in a parental antibody with a larger amino acid (e.g., T366Y or T366W); "Holes" or "cavities" are created by replacing a larger residue in a parental antibody with a smaller amino acid (e.g., Y407T, T366S, L368A and/or Y407V). In one embodiment, a heavy chain polypeptide containing a knob comprises T366W and S354C substitutions, numbered according to the Eu numbering system. In one embodiment, a heavy chain polypeptide containing a hole comprises T366S, L368A, Y407V and Y349C substitutions, numbered according to the Eu numbering system. In one embodiment, the multispecific antibody molecule disclosed herein comprises a first heavy chain polypeptide and a second heavy chain polypeptide, wherein the first heavy chain polypeptide comprises T366W and S354C substitutions, numbered according to the Eu numbering system, and the second heavy chain polypeptide comprises T366S, L368A, Y407V and Y349C substitutions, numbered according to the Eu numbering system.

Strand Exchange Engineered Domains (SEED)

SEED is based on sequence exchanges between IgG1 and IgA to create non-identical chains which heterodimerize preferentially. Alternating sequences from human IgA and IgG in the SEED CH3 domains generate two asymmetric but complementary domains, designated AG

and GA. The SEED design allows efficient generation of AG/GA heterodimers, while disfavoring homodimerization of AG and GA SEED CH3 domains.

Common Light Chain & CrossMab

Light chain mispairing must be avoided to generate homogenous preparations of bispecific IgGs. One way to achieve this is through the use of the common light chain principle, i.e. combining two binders that share one light chain but still have separate specificities. Another option is the CrossMab technology which avoids non-specific L chain mispairing by exchanging CH1 and CL domains in the Fab of one half of the bispecific antibody. Such crossover variants retain binding specificity and affinity, but make the two arms so different that L chain mispairing is prevented.

Antibody-Based Fusions

A variety of formats can be generated which contain additional binding entities attached to the N or C terminus of antibodies. These fusions with single chain or disulfide stabilized Fvs or Fabs result in the generation of tetravalent molecules with bivalent binding specificity for each antigen. Combinations of scFvs and scFabs with IgGs enable the production of molecules which can recognize three or more different antigens.

Antibody-Fab Fusion

Antibody-Fab fusions are bispecific antibodies comprising a traditional antibody to a first target and a Fab to a second target fused to the C terminus of the antibody heavy chain. Commonly the antibody and the Fab will have a common light chain. Antibody fusions can be produced by *(1)* engineering the DNA sequence of the target fusion, and *(2)* transfecting the target DNA into a suitable host cell to express the fusion protein. It seems like the antibody-scFv fusion may be linked by a (Gly)-Ser linker between the C-terminus of the CH3 domain and the N-terminus of the scFv, as described by Coloma, J. *et al.* (1997) *Nature Biotech* 15:159.

Antibody-scFv Fusion

*Antibody-scFv Fusion*s are bispecific antibodies comprising a traditional antibody and a scFv of unique specificity fused to the C terminus of the antibody heavy chain. The scFv can be

fused to the C terminus through the Heavy Chain of the scFv either directly or through a linker peptide. Antibody fusions can be produced by *(1)* engineering the DNA sequence of the target fusion, and *(2)* transfecting the target DNA into a suitable host cell to express the fusion protein. It seems like the antibody-scFv fusion may be linked by a (Gly)-Ser linker between the C-terminus of the CH3 domain and the N-terminus of the scFv, as described by Coloma, J. *et al.* (1997) *Nature Biotech* 15:159.

Variable Domain Immunoglobulin DVD

A related format is the dual variable domain immunoglobulin (DVD), which are composed of VH and VL domains of a second specificity place upon the N termini of the V domains by shorter linker sequences.

Fc-containing entities (mini-antibodies)

Fc-containing entities, also known as mini-antibodies, can be generated by fusing scFv to the C-termini of constant heavy region domain 3 (CH3-scFv) and/or to the hinge region (scFv-hinge-Fc) of an antibody with a different specificity. Trivalent entities can also be made which have disulfide stabilized variable domains (without peptide linker) fused to the C-terminus of CH3 domains of IgGs.

Fc-containing multispecific molecules

In some embodiments, the multispecific molecules disclosed herein includes an immunoglobulin constant region (e.g., an Fc region). Exemplary Fc regions can be chosen from the heavy chain constant regions of IgG1, IgG2, IgG3 or IgG4; more particularly, the heavy chain constant region of human IgG1, IgG2, IgG3, or IgG4.

In some embodiments, the immunoglobulin chain constant region (e.g., the Fc region) is altered, e.g., mutated, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function.

In other embodiments, an interface of a first and second immunoglobulin chain constant regions (e.g., a first and a second Fc region) is altered, e.g., mutated, to increase or decrease dimerization, e.g., relative to a non-engineered interface, e.g., a naturally-occurring interface. For example, dimerization of the immunoglobulin chain constant region (e.g., the Fc region) can

be enhanced by providing an Fc interface of a first and a second Fc region with one or more of: a paired protuberance-cavity ("knob-in-a hole"), an electrostatic interaction, or a strand-exchange, such that a greater ratio of heteromultimer to homomultimer forms, e.g., relative to a non-engineered interface.

In some embodiments, the multispecific molecules include a paired amino acid substitution at a position chosen from one or more of 347, 349, 350, 351, 366, 368, 370, 392, 394, 395, 397, 398, 399, 405, 407, or 409, e.g., of the Fc region of human IgG1 For example, the immunoglobulin chain constant region (e.g., Fc region) can include a paired an amino acid substitution chosen from: T366S, L368A, or Y407V (e.g., corresponding to a cavity or hole), and T366W (e.g., corresponding to a protuberance or knob).

In some embodiments, the immunoglobulin chain constant region (e.g., the Fc region) is not altered, e.g., not mutated, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function. In some embodiments, the multispecific molecules does not include a paired amino acid substitution at a position chosen from one or more of 347, 349, 350, 351, 366, 368, 370, 392, 394, 395, 397, 398, 399, 405, 407, or 409, e.g., of the Fc region of human IgG1 For example, the immunoglobulin chain constant region (e.g., Fc region) does not include a paired amino acid substitution chosen from: T366S, L368A, or Y407V (e.g., corresponding to a cavity or hole), and T366W (e.g., corresponding to a protuberance or knob).

In other embodiments, the multispecific molecule includes a half-life extender, e.g., a human serum albumin or an antibody molecule to human serum albumin.

Multispecific molecules comprising non-contiguous polypeptides

In one embodiment, the multispecific molecule is not a single polypeptide chain.

In one embodiment, the antibody molecule includes two, complete heavy chains and two, complete light chains. In one embodiment, the multispecific molecules having at least two or at least three non-contiguous polypeptide chains include a first and second immunoglobulin chain constant regions (e.g., a first and second Fc region) in at least two non-contiguous polypeptide chains, e.g., as described herein.

In embodiments, the multispecific molecule is a bispecific or bifunctional molecule, wherein the first and second polypeptides (i) and (ii) are non-contiguous, e.g., are two separate polypeptide chains. In some embodiments, the first and second polypeptides (i) and (ii) include a paired amino acid substitution at a position chosen from one or more of 347, 349, 350, 351, 366, 368, 370, 392, 394, 395, 397, 398, 399, 405, 407, or 409, e.g., of the Fc region of human IgG1. For example, the first immunoglobulin chain constant region (e.g., the first Fc region) can include an amino acid substitution chosen from: T366S, L368A, or Y407V (e.g., corresponding to a cavity or hole), and the second immunoglobulin chain constant region (e.g., the second Fc region) includes a T366W (e.g., corresponding to a protuberance or knob). In some embodiments, the first and second polypeptides are a first and second member of a heterodimeric first and second Fc region.

In embodiments, the multispecific molecule is a bispecific or bifunctional molecule, wherein the first and second polypeptides (i) and (ii) are non-contiguous, e.g., are two separate polypeptide chains. In some embodiments, the first and second polypeptides (i) and (ii) do not include a paired amino acid substitution at a position chosen from one or more of 347, 349, 350, 351, 366, 368, 370, 392, 394, 395, 397, 398, 399, 405, 407, or 409, e.g., of the Fc region of human IgG1.

In some embodiments, the first polypeptide has the following configuration from N-to-C:

(a) a first portion of a first antigen domain, e.g., a first VH-CH1 of a Fab molecule, that binds to a first antigen, e.g., a cancer antigen, e.g., a solid tumor, stromal or hematological antigen, connected, optionally via a linker to, the first immunoglobulin constant region (e.g., the CH2 connected to the CH3 region) (e.g., a first Fc region);

(b) a first portion of a second antigen domain, e.g., a first VH-CH1 of a Fab molecule, that binds to a second antigen, e.g., a cancer antigen, e.g., a solid tumor, stromal or hematological antigen, connected, optionally via a linker to, the first immunoglobulin constant region (e.g., the CH2 connected to the CH3 region) (e.g., a first Fc region);

(c) the third polypeptide has the following configuration from N-to-C: a second portion of the first antigen domain, e.g., a first VL-CL of the Fab, where the VL is of kappa subtype and binds to a first antigen, e.g., a cancer antigen, e.g., a solid tumor, stromal or hematological antigen (e.g., the same cancer antigen bound by the first VH-CH1);

(d) the fourth polypeptide has the following configuration from N-to-C: a second portion of the second antigen domain, e.g. a second VL-CL of the Fab, where the VL is of lambda subtype and binds to a second antigen, e.g., a cancer antigen, e.g., a solid tumor, stromal, or hematological antigen (e.g., the same cancer antigen bound by the second VH-CH1) (e.g. an example of this configuration is depicted in **FIG. 1A**).

In embodiments, the first immunoglobulin constant region (e.g., the first CH2-CH3 region) includes a protuberance or knob, e.g., as described herein. In embodiments, the first immunoglobulin constant region (e.g., the first CH2-CH3 region) does not include a protuberance or knob, e.g., as described herein.

In embodiments, the second immunoglobulin constant region (e.g., the second CH2-CH3 region) includes a cavity or hole. In embodiments, the first and second immunoglobulin constant region promote heterodimerization of the bispecific molecule. In embodiments, the second immunoglobulin constant region (e.g., the second CH2-CH3 region) does not include a cavity or hole. In embodiments, the first and second immunoglobulin constant region does not promote heterodimerization of the bispecific molecule.

Tumor Specific Targeting Moieties

In certain embodiments, the multispecific antibody molecules disclosed herein include a tumor-targeting moiety. The tumor targeting moiety can be chosen from an antibody molecule (e.g., an antigen binding domain as described herein), a receptor or a receptor fragment, or a ligand or a ligand fragment, or a combination thereof. In some embodiments, the tumor targeting moiety associates with, e.g., binds to, a tumor cell (e.g., a molecule, e.g., antigen, present on the surface of the tumor cell). In certain embodiments, the tumor targeting moiety targets, e.g., directs the multispecific molecules disclosed herein to a cancer (e.g., a cancer or tumor cells). In some embodiments, the cancer is chosen from a hematological cancer, a solid cancer, a metastatic cancer, or a combination thereof.

In some embodiments, the multispecific molecule, e.g., the tumor-targeting moiety, binds to a solid tumor antigen or a stromal antigen. The solid tumor antigen or stromal antigen can be present on a solid tumor, or a metastatic lesion thereof. In some embodiments, the solid tumor is chosen from one or more of pancreatic (*e.g.*, pancreatic adenocarcinoma), breast, colorectal, lung (*e.g.*, small or non-small cell lung cancer), skin, ovarian, or liver cancer. In one embodiment, the solid tumor is a fibrotic or desmoplastic solid tumor. For example, the solid tumor antigen or

stromal antigen can be present on a tumor, e.g., a tumor of a class typified by having one or more of: limited tumor perfusion, compressed blood vessels, or fibrotic tumor interstitium.

In certain embodiments, the solid tumor antigen is chosen from one or more of: mesothelin, gangloside 2 (GD2), prostate stem cell antigen (PSCA), prostate specific membrane antigen (PMSA), prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), Ron Kinase, c-Met, Immature laminin receptor, TAG-72, BING-4, Calcium-activated chloride channel 2, Cyclin-B1, 9D7, Ep-CAM, EphA3, Her2/neu, Telomerase, SAP-1, Survivin, NY-ESO-1/LAGE-1, PRAME, SSX-2, Melan-A/MART-1, Gp100/pmel17, Tyrosinase, TRP-1/-2, MC1R, β-catenin, BRCA1/2, CDK4, CML66, Fibronectin, p53, Ras, TGF-B receptor, AFP, ETA, MAGE, MUC-1, CA-125, BAGE, GAGE, NY-ESO-1, β-catenin, CDK4, CDC27, α actinin-4, TRP1/gp75, TRP2, gp100, Melan-A/MART1, gangliosides, WT1, EphA3, Epidermal growth factor receptor (EGFR), CD20, MART-2, MART-1, MUC1, MUC2, MUM1, MUM2, MUM3, NA88-1, NPM, OA1, OGT, RCC, RUI1, RUI2, SAGE, TRG, TRP1, or TSTA. In some embodiments, the solid tumor antigen is chosen from: Mesothelin, GD2, PMSA, PSCA, CEA, Ron Kinase, or c-Met. In some embodiments, the solid tumor antigen is Mesothelin.

Cytokine Molecules

In certain embodiments, the multispecific antibody molecules disclosed herein can further include a cytokine molecule.

Cytokines are proteinaceous signaling compounds that are mediators of the immune response. They control many different cellular functions including proliferation, differentiation and cell survival/apoptosis; cytokines are also involved in several pathophysiological processes including viral infections and autoimmune diseases. Cytokines are synthesized under various stimuli by a variety of cells of both the innate (monocytes, macrophages, dendritic cells) and adaptive (T- and B-cells) immune systems. Cytokines can be classified into two groups: pro- and anti-inflammatory. Pro-inflammatory cytokines, including IFNgamma, IL-1, IL-6 and TNF-alpha, are predominantly derived from the innate immune cells and Th1 cells. Anti-inflammatory cytokines, including IL-10, IL-4, IL-13 and IL-5, are synthesized from Th2 immune cells.

The present disclosure provides, *inter alia*, multi-specific (e.g., bi-, tri-, quad- specific) proteins, that include, e.g., are engineered to contain, one or more cytokine molecules, e.g., immunomodulatory (e.g., proinflammatory) cytokines and variants, e.g., functional variants,

thereof. Accordingly, in some embodiments, the cytokine molecule is an interleukin or a variant, e.g., a functional variant thereof. In some embodiments the interleukin is a proinflammatory interleukin. In some embodiments the interleukin is chosen from interleukin-2 (IL-2), interleukin-12 (IL-12), interleukin-15 (IL-15), interleukin-18 (IL-18), interleukin-21 (IL-21), or interferon gamma. In some embodiments the interleukin is interleukin-2 (IL-2). In some embodiments, the cytokine molecule is a proinflammatory cytokine.

In some embodiments, the multispecific molecules disclosed herein include a cytokine molecule. In embodiments, the cytokine molecule includes a full length, a fragment or a variant of a cytokine; a cytokine receptor domain, e.g., a cytokine receptor dimerizing domain; or an agonist of a cytokine receptor, e.g., an antibody molecule (e.g., an agonistic antibody) to a cytokine receptor.

In some embodiments the cytokine molecule is chosen from IL-2, IL-12, IL-15, IL-18, IL-21, or interferon gamma, or a fragment or variant thereof, or a combination of any of the aforesaid cytokines. The cytokine molecule can be a monomer or a dimer. In embodiments, the cytokine molecule can further include a cytokine receptor dimerizing domain.

In other embodiments, the cytokine molecule is an agonist of a cytokine receptor, e.g., an antibody molecule (e.g., an agonistic antibody) to a cytokine receptor chosen from an IL-15Ra or IL-21R.

Immune Cell Engagers

In certain embodiments, the multispecific antibody molecules disclosed herein can include an immune cell engager.

The immune cell engagers of the multispecific molecules disclosed herein can mediate binding to, and/or activation of, an immune cell, e.g., an immune effector cell. In some embodiments, the immune cell is chosen from an NK cell, a B cell, a dendritic cell, or a macrophage cell engager, or a combination thereof. In some embodiments, the immune cell engager is chosen from one, two, three, or all of an NK cell engager, a B cell engager, a dendritic cell engager, or a macrophage cell engager, or a combination thereof. The immune cell engager can be an agonist of the immune system. In some embodiments, the immune cell engager can be an antibody molecule, a ligand molecule (e.g., a ligand that further comprises an immunoglobulin constant region, e.g., an Fc region), a small molecule, a nucleotide molecule.

Natural Killer Cell Engagers

Natural Killer (NK) cells recognize and destroy tumors and virus-infected cells in an antibody-independent manner. The regulation of NK cells is mediated by activating and inhibiting receptors on the NK cell surface. One family of activating receptors is the natural cytotoxicity receptors (NCRs) which include NKp30, NKp44 and NKp46. The NCRs initiate tumor targeting by recognition of heparan sulfate on cancer cells. NKG2D is a receptor that provides both stimulatory and costimulatory innate immune responses on activated killer (NK) cells, leading to cytotoxic activity. DNAM1 is a receptor involved in intercellular adhesion, lymphocyte signaling, cytotoxicity and lymphokine secretion mediated by cytotoxic T-lymphocyte (CTL) and NK cell. DAP10 (also known as HCST) is a transmembrane adapter protein which associates with KLRK1 to form an activation receptor KLRK1-HCST in lymphoid and myeloid cells; this receptor plays a major role in triggering cytotoxicity against target cells expressing cell surface ligands such as MHC class I chain-related MICA and MICB, and U(optionally L1)6-binding proteins (ULBPs); it KLRK1-HCST receptor plays a role in immune surveillance against tumors and is required for cytolysis of tumors cells; indeed, melanoma cells that do not express KLRK1 ligands escape from immune surveillance mediated by NK cells. CD16 is a receptor for the Fc region of IgG, which binds complexed or aggregated IgG and also monomeric IgG and thereby mediates antibody-dependent cellular cytotoxicity (ADCC) and other antibody-dependent responses, such as phagocytosis.

In some embodiments, the NK cell engager is a viral hemagglutinin (HA), HA is a glycoprotein found on the surface of influenza viruses. It is responsible for binding the virus to cells with sialic acid on the membranes, such as cells in the upper respiratory tract or erythrocytes. HA has at least 18 different antigens. These subtypes are named H1 through H18. NCRs can recognize viral proteins. NKp46 has been shown to be able to interact with the HA of influenza and the HA-NA of Paramyxovirus, including Sendai virus and Newcastle disease virus. Besides NKp46, NKp44 can also functionally interact with HA of different influenza subtypes.

The present disclosure provides, *inter alia*, multi-specific (e.g., bi-, tri-, quad- specific) proteins, that are engineered to contain one or more NK cell engager that mediate binding to and/or activation of an NK cell. Accordingly, in some embodiments, the NK cell engager is selected from an antigen binding domain or ligand that binds to (e.g., activates): NKp30, NKp40,

NKp44, NKp46, NKG2D, DNAM1, DAP10, CD16 (e.g., CD16a, CD16b, or both), CRTAM, CD27, PSGL1, CD96, CD100 (SEMA4D), NKp80 or CD244 (also known as SLAMF4 or 2B4). in some embodiments, the NK cell engager is selected from an antigen binding domain or ligand that binds to (e.g., activates): NKp30 or NKp46.

In other embodiments, the NK cell engager is a ligand of NKp44 or NKp46, which is a viral HA. Viral hemagglutinins (HA) are glyco proteins which are on the surface of viruses. HA proteins allow viruses to bind to the membrane of cells via sialic acid sugar moieties which contributes to the fusion of viral membranes with the cell membranes (see e.g., Eur J Immunol. 2001 Sep;31(9):2680-9 "Recognition of viral hemagglutinins by NKp44 but not by NKp30"; and Nature. 2001 Feb 22;409(6823):1055-60 "Recognition of haemagglutinins on virus-infected cells by NKp46 activates lysis by human NK cells" the contents of each of which are incorporated by reference herein).

In other embodiments, the NK cell engager is a ligand of NKG2D chosen from MICA, MICB, or ULBP1.

In other embodiments, the NK cell engager is a ligand of DNAM1 chosen from NECTIN2 or NECL5.

In yet other embodiments, the NK cell engager is a ligand of DAP10, which is an adapter for NKG2D (see e.g., Proc Natl Acad Sci U S A. 2005 May 24; 102(21): 7641–7646; and Blood, 15 September 2011 Volume 118, Number 11, the full contents of each of which is incorporated by reference herein).

In other embodiments, the NK cell engager is a ligand of CD16, which is a CD16a/b ligand, e.g., a CD16a/b ligand further comprising an antibody Fc region (see e.g., Front Immunol. 2013; 4: 76 discusses how antibodies use the Fc to trigger NK cells through CD16,the full contents of which are incorporated herein).

B Cell, Macrophage & Dendritic Cell Engagers

Broadly, B cells, also known as B lymphocytes, are a type of white blood cell of the lymphocyte subtype. They function in the humoral immunity component of the adaptive immune system by secreting antibodies. Additionally, B cells present antigen (they are also classified as professional antigen-presenting cells (APCs)) and secrete cytokines. Macrophages are a type of white blood cell that engulfs and digests cellular debris, foreign substances, microbes, cancer

cells via phagocytosis. Besides phagocytosis, they play important roles in nonspecific defense (innate immunity) and also help initiate specific defense mechanisms (adaptive immunity) by recruiting other immune cells such as lymphocytes. For example, they are important as antigen presenters to T cells. Beyond increasing inflammation and stimulating the immune system, macrophages also play an important anti-inflammatory role and can decrease immune reactions through the release of cytokines. Dendritic cells (DCs) are antigen-presenting cells that function in processing antigen material and present it on the cell surface to the T cells of the immune system.

The present disclosure provides, *inter alia*, multi-specific (e.g., bi-, tri-, quad- specific) proteins, that include, e.g., are engineered to contain, one or more B cell, macrophage, and/or dendritic cell engager that mediate binding to and/ or activation of a B cell, macrophage, and/or dendritic cell.

Accordingly, in some embodiments, the immune cell engager comprises a B cell, macrophage, and/or dendritic cell engager chosen from one or more of CD40 ligand (CD40L) or a CD70 ligand; an antibody molecule that binds to CD40 or CD70; an antibody molecule to OX40; an OX40 ligand (OX40L); an agonist of a Toll-like receptor (e.g., as described herein, e.g., a TLR4, e.g., a constitutively active TLR4 (caTLR4), or a TLR9 agonists); a 41BB; a CD2; a CD47; or a STING agonist, or a combination thereof.

In some embodiments, the B cell engager is a CD40L, an OX40L, or a CD70 ligand, or an antibody molecule that binds to OX40, CD40 or CD70.

In some embodiments, the macrophage engager is a CD2 agonist. In some embodiments, the macrophage engager is an antigen binding domain that binds to: CD40L or antigen binding domain or ligand that binds CD40, a Toll like receptor (TLR) agonist (e.g., as described herein), e.g., a TLR9 or TLR4 (e.g., caTLR4 (constitutively active TLR4), CD47, or a STING agonist. In some embodiments, the STING agonist is a cyclic dinucleotide, e.g., cyclic di-GMP (cdGMP) or cyclic di-AMP (cdAMP). In some embodiments, the STING agonist is biotinylated.

In some embodiments, the dendritic cell engager is a CD2 agonist. In some embodiments, the dendritic cell engager is a ligand, a receptor agonist, or an antibody molecule that binds to one or more of: OX40L, 41BB, a TLR agonist (e.g., as described herein) (e.g., TLR9 agonist, TLR4 (e.g., caTLR4 (constitutively active TLR4)), CD47, or and a STING agonist. In some

embodiments, the STING agonist is a cyclic dinucleotide, e.g., cyclic di-GMP (cdGMP) or cyclic di-AMP (cdAMP). In some embodiments, the STING agonist is biotinylated.

In other embodiments, the immune cell engager mediates binding to, or activation of, one or more of a B cell, a macrophage, and/or a dendritic cell. Exemplary B cell, macrophage, and/or dendritic cell engagers can be chosen from one or more of CD40 ligand (CD40L) or a CD70 ligand; an antibody molecule that binds to CD40 or CD70; an antibody molecule to OX40; an OX40 ligand (OX40L); a Toll-like receptor agonist (e.g., a TLR4, e.g., a constitutively active TLR4 (caTLR4) or a TLR9 agonist); a 41BB agonist; a CD2; a CD47; or a STING agonist, or a combination thereof.

In some embodiments, the B cell engager is chosen from one or more of a CD40L, an OX40L, or a CD70 ligand, or an antibody molecule that binds to OX40, CD40 or CD70.

In other embodiments, the macrophage cell engager is chosen from one or more of a CD2 agonist; a CD40L; an OX40L; an antibody molecule that binds to OX40, CD40 or CD70; a Toll-like receptor agonist or a fragment thereof (e.g., a TLR4, e.g., a constitutively active TLR4 (caTLR4)); a CD47 agonist; or a STING agonist.

In other embodiments, the dendritic cell engager is chosen from one or more of a CD2 agonist, an OX40 antibody, an OX40L, 41BB agonist, a Toll-like receptor agonist or a fragment thereof (e.g., a TLR4, e.g., a constitutively active TLR4 (caTLR4)), CD47 agonist, or a STING agonist.

In yet other embodiments, the STING agonist comprises a cyclic dinucleotide, e.g., a cyclic di-GMP (cdGMP), a cyclic di-AMP (cdAMP), or a combination thereof, optionally with 2',5' or 3',5' phosphate linkages.

Toll-Like Receptors

Toll-Like Receptors (TLRs) are evolutionarily conserved receptors are homologues of the Drosophila Toll protein, and recognize highly conserved structural motifs known as pathogen-associated microbial patterns (PAMPs), which are exclusively expressed by microbial pathogens, or danger-associated molecular patterns (DAMPs) that are endogenous molecules released from necrotic or dying cells. PAMPs include various bacterial cell wall components such as lipopolysaccharide (LPS), peptidoglycan (PGN) and lipopeptides, as well as flagellin, bacterial DNA and viral double-stranded RNA. DAMPs include intracellular proteins such as heat shock

proteins as well as protein fragments from the extracellular matrix. Stimulation of TLRs by the corresponding PAMPs or DAMPs initiates signaling cascades leading to the activation of transcription factors, such as AP-1, NF-κB and interferon regulatory factors (IRFs). Signaling by TLRs results in a variety of cellular responses, including the production of interferons (IFNs), pro-inflammatory cytokines and effector cytokines that direct the adaptive immune response. TLRs are implicated in a number of inflammatory and immune disorders and play a role in cancer (Rakoff-Nahoum S. & Medzhitov R., 2009. Toll-like receptors and cancer. Nat Revs Cancer 9:57- 63.)

TLRs are type I transmembrane proteins characterized by an extracellular domain containing leucine-rich repeats (LRRs) and a cytoplasmic tail that contains a conserved region called the Toll/IL-1 receptor (TIR) domain. Ten human and twelve murine TLRs have been characterized, TLR1 to TLR10 in humans, and TLR1 to TLR9, TLR11, TLR12 and TLR13 in mice, the homolog of TLR10 being a pseudogene. TLR2 is essential for the recognition of a variety of PAMPs from Gram-positive bacteria, including bacterial lipoproteins, lipomannans and lipoteichoic acids. TLR3 is implicated in virus-derived double-stranded RNA. TLR4 is predominantly activated by lipopolysaccharide. TLR5 detects bacterial flagellin and TLR9 is required for response to unmethylated CpG DNA. Finally, TLR7 and TLR8 recognize small synthetic antiviral molecules, and single-stranded RNA was reported to be their natural ligand. TLR11 has been reported to recognize uropathogenic E.coli and a profilin-like protein from Toxoplasma gondii. The repertoire of specificities of the TLRs is apparently extended by the ability of TLRs to heterodimerize with one another. For example, dimers of TLR2 and TLR6 are required for responses to diacylated lipoproteins while TLR2 and TLR1 interact to recognize triacylated lipoproteins. Specificities of the TLRs are also influenced by various adapter and accessory molecules, such as MD-2 and CD14 that form a complex with TLR4 in response to LPS.

TLR signaling consists of at least two distinct pathways: a MyD88-dependent pathway that leads to the production of inflammatory cytokines, and a MyD88-independent pathway associated with the stimulation of IFN-β and the maturation of dendritic cells. The MyD88-dependent pathway is common to all TLRs, except TLR3 (Adachi O. et al., 1998. Targeted disruption of the MyD88 gene results in loss of IL-1- and IL-18-mediated function. Immunity. 9(1):143-50). Upon activation by PAMPs or DAMPs, TLRs hetero- or homodimerize inducing

the recruitment of adaptor proteins via the cytoplasmic TIR domain. Individual TLRs induce different signaling responses by usage of the different adaptor molecules. TLR4 and TLR2 signaling requires the adaptor TIRAP/Mal, which is involved in the MyD88-dependent pathway. TLR3 triggers the production of IFN-β in response to double-stranded RNA, in a MyD88-independent manner, through the adaptor TRIF/TICAM-1. TRAM/TICAM-2 is another adaptor molecule involved in the MyD88-independent pathway which function is restricted to the TLR4 pathway.

TLR3, TLR7, TLR8 and TLR9 recognize viral nucleic acids and induce type I IFNs. The signaling mechanisms leading to the induction of type I IFNs differ depending on the TLR activated. They involve the interferon regulatory factors, IRFs, a family of transcription factors known to play a critical role in antiviral defense, cell growth and immune regulation. Three IRFs (IRF3, IRF5 and IRF7) function as direct transducers of virus-mediated TLR signaling. TLR3 and TLR4 activate IRF3 and IRF7, while TLR7 and TLR8 activate IRF5 and IRF7 (Doyle S. et al., 2002. IRF3 mediates a TLR3/TLR4-specific antiviral gene program. Immunity. 17(3):251-63). Furthermore, type I IFN production stimulated by TLR9 ligand CpG-A has been shown to be mediated by PI(3)K and mTOR (Costa-Mattioli M. & Sonenberg N. 2008. RAPping production of type I interferon in pDCs through mTOR. Nature Immunol. 9: 1097-1099).

TLR-9

TLR9 recognizes unmethylated CpG sequences in DNA molecules. CpG sites are relatively rare (~1%) on vertebrate genomes in comparison to bacterial genomes or viral DNA. TLR9 is expressed by numerous cells of the immune system such as B lymphocytes, monocytes, natural killer (NK) cells, and plasmacytoid dendritic cells. TLR9 is expressed intracellularly, within the endosomal compartments and functions to alert the immune system of viral and bacterial infections by binding to DNA rich in CpG motifs. TLR9 signals leads to activation of the cells initiating pro-inflammatory reactions that result in the production of cytokines such as type-I interferon and IL-12.

TLR Agonists

A TLR agonist can agonize one or more TLR, e.g., one or more of human TLR- 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, an adjunctive agent described herein is a TLR

agonist. In some embodiments, the TLR agonist specifically agonizes human TLR-9. In some embodiments, the TLR-9 agonist is a CpG moiety. As used herein, a CpG moiety, is a linear dinucleotide having the sequence: 5'—C—phosphate—G—3', that is, cytosine and guanine separated by only one phosphate.

In some embodiments, the CpG moiety comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more CpG dinucleotides. In some embodiments, the CpG moiety consists of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 CpG dinucleotides. In some embodiments, the CpG moiety has 1-5, 1-10, 1-20, 1-30, 1-40, 1-50, 5-10, 5-20, 5-30, 10-20, 10-30, 10-40, or 10-50 CpG dinucleotides.

In some embodiments, the TLR-9 agonist is a synthetic ODN (oligodeoxynucleotides). CpG ODNs are short synthetic single-stranded DNA molecules containing unmethylated CpG dinucleotides in particular sequence contexts (CpG motifs). CpG ODNs possess a partially or completely phosphorothioated (PS) backbone, as opposed to the natural phosphodiester (PO) backbone found in genomic bacterial DNA. There are three major classes of CpG ODNs: classes A, B and C, which differ in their immunostimulatory activities. CpG-A ODNs are characterized by a PO central CpG-containing palindromic motif and a PS-modified 3' poly-G string. They induce high IFN-α production from pDCs but are weak stimulators of TLR9-dependent NF-κB signaling and pro-inflammatory cytokine (e.g. IL-6) production. CpG-B ODNs contain a full PS backbone with one or more CpG dinucleotides. They strongly activate B cells and TLR9-dependent NF-κB signaling but weakly stimulate IFN-α secretion. CpG-C ODNs combine features of both classes A and B. They contain a complete PS backbone and a CpG-containing palindromic motif. C-Class CpG ODNs induce strong IFN-α production from pDC as well as B cell stimulation.

Exemplary multispecific antibody molecules

Exemplary kappa and lambda multispecific antibody molecules are provided in Tables 17 and 18.

Table 17. Exemplary amino acid sequences of antibodies

Target	Antibody	Heavy Chain Variable Domain Sequence	Light Chain Variable Domain Sequence
Rabphilin	Ab237	SEQ ID NO: 401	SEQ ID NO 402:

3A		QVQLQESGPGLVKPSQTLSLTCTV SGGSINNNNYYWTWIRQHPGKGLE WIGYIYYSGSTFYNPSLKSRVTIS VDTSKTQFSLKLSSVTAADTAVYY CAREDTMTGLDVWGQGTTVTVSS	DIQMTQSPSSLSASVGDRVTIT CRASQSINNYLNWYQQKPGKAP TLLIYAASSLQSGVPSRFSGSR SGTDFTLTISSLQPEDFAAYFC QQTYSNPTFGQGTKVEVK
PD-L1	Avelumab	SEQ ID NO 403: EVQLLESGGGLVQPGGSLRLSCAA SGFTFSSYIMMWVRQAPGKGLEWV SSIYPSGGITFYADTVKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYC ARIKLGTVTTVDYWGQGTLVTVSS	SEQ ID NO 404: QSALTQPASVSGSPGQSITISC TGTSSDVGGYNYVSWYQQHPGK APKLMIYDVSNRPSGVSNRFSG SKSGNTASLTISGLQAEDEADY YCSSYTSSSTRVFGTGTKVTVL
CTLA-4	Ipilumumab	SEQ ID NO 405: QVQLVESGGGVVQPGRSLRLSCAA SGFTFSSYTMHWVRQAPGKGLEWV TFISYDGNNKYYADSVKGRFTISR DNSKNTLYLQMNSLRAEDTAIYYC ARTGWLGPFDYWGQGTLVTVSS	SEQ ID NO 406: EIVLTQSPGTLSLSPGERATLS CRASQSVGSSYLAWYQQKPGQA PRLLIYGAFSRATGIPDRFSGS GSGTDFTLTISRLEPEDFAVYY CQQYGSSPWTFGQGTKVEIK
IL-12/23	Briakinumab	SEQ ID NO 407: QVQLVESGGGVVQPGRSLRLSCAA SGFTFSSYGMHWVRQAPGKGLEWV AFIRYDGSNKYYADSVKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYC KTHGSHDNWGQGTMVTVSS	SEQ ID NO 408: QSVLTQPPSVSGAPGQRVTISC SGSRSNIGSNTVKWYQQLPGTA PKLLIYYNDQRPSGVPDRFSGS KSGTSASLAITGLQAEDEADYY CQSYDRYTHPALLFGTGTKVTV L
PD-1	Nivolumab	SEQ ID NO 409: QVQLVESGGGVVQPGRSLRLDCKA SGITFSNSGMHWVRQAPGKGLEWV AVIWYDGSKRYYADSVKGRFTISR DNSKNTLFLQMNSLRAEDTAVYYC ATNDDYWGQGTLVTVSS	SEQ ID NO 410: EIVLTQSPATLSLSPGERATLS CRASQSVSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSG SGTDFTLTISSLEPEDFAVYYC QQSSNWPRTFGQGTKVEIK
TRAIL-R2	Lexatumumab	SEQ ID NO 411: EVQLVQSGGGVERPGGSLRLSCAA SGFTFDDYGMSWVRQAPGKGLEWV SGINWNGGSTGYADSVKGRVTISR DNAKNSLYLQMNSLRAEDTAVYYC AKILGAGRGWYFDLWGKGTTVTVS S	SEQ ID NO 412: SSELTQDPAVSVALGQTVRITC QGDSLRSYYASWYQQKPGQAPV LVIYGKNNRPSGIPDRFSGSSS GNTASLTITGAQAEDEADYYCN SRDSSGNHVVFGGGTKLTVL
CD20	Ofatumumab	SEQ ID NO 413: EVQLVESGGGLVQPGRSLRLSCAA SGFTFNDYAMHWVRQAPGKGLEWV STISWNSGSIGYADSVKGRFTISR DNAKKSLYLQMNSLRAEDTALYYC AKDIQYGNYYYGMDVWGQGTTVTV SS	SEQ ID NO 414: EIVLTQSPATLSLSPGERATLS CRASQSVSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSG SGTDFTLTISSLEPEDFAVYYC QQRSNWPITFGQGTRLEIK
IGF-1R	Cixutumumab	SEQ ID NO 415: EVQLVQSGAEVKKPGSSVKVSCKA SGGTFSSYAISWVRQAPGQGLEWM GGIIPIFGTANYAQKFQGRVTITA DKSTSTAYMELSSLRSEDTAVYYC ARAPLRFLEWSTQDHYYYYYMDVW GKGTTVTVSS	SEQ ID NO 416: SSELTQDPAVSVALGQTVRITC QGDSLRSYYATWYQQKPGQAPI LVIYGENKRPSGIPDRFSGSSS GNTASLTITGAQAEDEADYYCK SRDGSGQHLVFGGGTKLTVL

Mesothelin	m912	SEQ ID NO: 417 QVQLQESGPGLVKPSETLSLTCTV SGGSVSSGSYYWSWIRQPPGKGLE WIGYIYYSGSTNYNPSLKSRVTIS VDTSKNQFSLKLSSVTAADTAVYY CAREGKNGAFDIWGQGTMVTVSS	SEQ ID NO: 418 DIQMTQSPSSLSASVGDRVTIT CRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSGFSGSG SGTDFTLTISSLQPEDFATYYC QQSYSTPLTFGGGTKVEIK

Table 18. Exemplary pairings of kappa and lambda antibodies

	Lambda Antibodies			
Kappa Antibodies	**Avelumab**	**Briakinumab**	**Lexatumumab**	**Cixutumumab**
Ab237	SEQ ID NO: 401, SEQ ID NO: 402, SEQ ID NO: 403, SEQ ID NO: 404	SEQ ID NO: 401, SEQ ID NO: 402, SEQ ID NO: 407, SEQ ID NO: 408	SEQ ID NO: 401, SEQ ID NO: 402, SEQ ID NO: 411, SEQ ID NO: 412	SEQ ID NO: 401, SEQ ID NO: 402, SEQ ID NO: 415, SEQ ID NO: 416
Ipilumumab	SEQ ID NO: 405, SEQ ID NO: 406, SEQ ID NO: 403, SEQ ID NO: 404	SEQ ID NO: 405, SEQ ID NO: 406, SEQ ID NO: 407, SEQ ID NO: 408	SEQ ID NO: 405, SEQ ID NO: 406, SEQ ID NO: 411, SEQ ID NO: 412	SEQ ID NO: 405, SEQ ID NO: 406, SEQ ID NO: 415, SEQ ID NO: 416
Nivolumab	SEQ ID NO: 409, SEQ ID NO: 410, SEQ ID NO: 403, SEQ ID NO: 404	SEQ ID NO: 409, SEQ ID NO: 410, SEQ ID NO: 407, SEQ ID NO: 408	SEQ ID NO: 409, SEQ ID NO: 410, SEQ ID NO: 411, SEQ ID NO: 412	SEQ ID NO: 409, SEQ ID NO: 410, SEQ ID NO: 415, SEQ ID NO: 416
Ofatumumab	SEQ ID NO: 413, SEQ ID NO: 414, SEQ ID NO: 403, SEQ ID NO: 404	SEQ ID NO: 413, SEQ ID NO: 414, SEQ ID NO: 407, SEQ ID NO: 408	SEQ ID NO: 413, SEQ ID NO: 414, SEQ ID NO: 411, SEQ ID NO: 412	SEQ ID NO: 413, SEQ ID NO: 414, SEQ ID NO: 415, SEQ ID NO: 416
m912	SEQ ID NO: 417, SEQ ID NO: 418, SEQ ID NO: 403, SEQ ID NO: 404	SEQ ID NO: 417, SEQ ID NO: 418, SEQ ID NO: 407, SEQ ID NO: 408	SEQ ID NO: 417, SEQ ID NO: 418, SEQ ID NO: 411, SEQ ID NO: 412	SEQ ID NO: 417, SEQ ID NO: 418, SEQ ID NO: 415, SEQ ID NO: 416

Nucleic Acids

The invention also features nucleic acids comprising nucleotide sequences that encode heavy and light chain variable regions and CDRs or hypervariable loops of the antibody molecules, as described herein. For example, the invention features a first and second nucleic acid encoding heavy and light chain variable regions, respectively, of an antibody molecule chosen from one or more of the antibody molecules disclosed herein. The nucleic acid can comprise a nucleotide sequence as set forth in the tables herein, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the sequences shown in the tables herein.

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs or hypervariable loops from a heavy chain variable region having an amino acid sequence as set forth in the tables herein, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one or more substitutions, *e.g.*, conserved substitutions). In other embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs or hypervariable loops from a light chain variable region having an amino acid sequence as set forth in the tables herein, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one or more substitutions, *e.g.*, conserved substitutions). In yet another embodiment, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, three, four, five, or six CDRs or hypervariable loops from heavy and light chain variable regions having an amino acid sequence as set forth in the tables herein, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one or more substitutions, *e.g.*, conserved substitutions).

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs or hypervariable loops from a heavy chain variable region having the nucleotide sequence as set forth in the tables herein, a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein). In another embodiment, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs or hypervariable loops from a light chain variable region having the nucleotide sequence as set forth in the tables herein, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein). In yet another embodiment, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, three, four, five, or six CDRs or hypervariable loops from heavy and light chain variable regions having the nucleotide sequence as set forth in the tables herein, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein).

In another aspect, the application features host cells and vectors containing the nucleic acids described herein. The nucleic acids may be present in a single vector or separate vectors present in the same host cell or separate host cell, as described in more detail hereinbelow.

Vectors

Further provided herein are vectors comprising the nucleotide sequences encoding an antibody molecule described herein. In one embodiment, the vectors comprise nucleotides encoding an antibody molecule described herein. In one embodiment, the vectors comprise the nucleotide sequences described herein. The vectors include, but are not limited to, a virus, plasmid, cosmid, lambda phage or a yeast artificial chromosome (YAC).

Numerous vector systems can be employed. For example, one class of vectors utilizes DNA elements which are derived from animal viruses such as, for example, bovine papilloma virus, polyoma virus, adenovirus, vaccinia virus, baculovirus, retroviruses (Rous Sarcoma Virus, MMTV or MOMLV) or SV40 virus. Another class of vectors utilizes RNA elements derived from RNA viruses such as Semliki Forest virus, Eastern Equine Encephalitis virus and Flaviviruses.

Additionally, cells which have stably integrated the DNA into their chromosomes may be selected by introducing one or more markers which allow for the selection of transfected host cells. The marker may provide, for example, prototropy to an auxotrophic host, biocide resistance (*e.g.,* antibiotics), or resistance to heavy metals such as copper, or the like. The selectable marker gene can be either directly linked to the DNA sequences to be expressed, or introduced into the same cell by cotransformation. Additional elements may also be needed for optimal synthesis of mRNA. These elements may include splice signals, as well as transcriptional promoters, enhancers, and termination signals.

Once the expression vector or DNA sequence containing the constructs has been prepared for expression, the expression vectors may be transfected or introduced into an appropriate host cell. Various techniques may be employed to achieve this, such as, for example, protoplast fusion, calcium phosphate precipitation, electroporation, retroviral transduction, viral transfection, gene gun, lipid based transfection or other conventional techniques. In the case of protoplast fusion, the cells are grown in media and screened for the appropriate activity.

Methods and conditions for culturing the resulting transfected cells and for recovering the

antibody molecule produced are known to those skilled in the art, and may be varied or optimized depending upon the specific expression vector and mammalian host cell employed, based upon the present description.

Cells

In another aspect, the application features host cells and vectors containing the nucleic acids described herein. The nucleic acids may be present in a single vector or separate vectors present in the same host cell or separate host cell. The host cell can be a eukaryotic cell, *e.g.*, a mammalian cell, an insect cell, a yeast cell, or a prokaryotic cell, *e.g.*, *E. coli*. For example, the mammalian cell can be a cultured cell or a cell line. Exemplary mammalian cells include lymphocytic cell lines (*e.g.*, NSO), Chinese hamster ovary cells (CHO), COS cells, oocyte cells, and cells from a transgenic animal, *e.g.*, mammary epithelial cell.

The invention also provides host cells comprising a nucleic acid encoding an antibody molecule as described herein.

In one embodiment, the host cells are genetically engineered to comprise nucleic acids encoding the antibody molecule.

In one embodiment, the host cells are genetically engineered by using an expression cassette. The phrase "expression cassette," refers to nucleotide sequences, which are capable of affecting expression of a gene in hosts compatible with such sequences. Such cassettes may include a promoter, an open reading frame with or without introns, and a termination signal. Additional factors necessary or helpful in effecting expression may also be used, such as, for example, an inducible promoter.

The invention also provides host cells comprising the vectors described herein.

The cell can be, but is not limited to, a eukaryotic cell, a bacterial cell, an insect cell, or a human cell. Suitable eukaryotic cells include, but are not limited to, Vero cells, HeLa cells, COS cells, CHO cells, HEK293 cells, BHK cells and MDCKII cells. Suitable insect cells include, but are not limited to, Sf9 cells.

Methods of Making the Multispecific Molecules

The multispecific antibody molecules can be produced by recombinant expression, e.g., of at least one or more component, in a host system. Exemplary host systems include eukaryotic

cells (e.g., mammalian cells, e.g., CHO cells, or insect cells, e.g., SF9 or S2 cells) and prokaryotic cells (e.g., *E. coli*). In one embodiment, the host cell is a mammalian cell, a stable mammalian cell, e.g., a CHO cell. Bispecific antibody molecules can be produced by separate expression of the components in different host cells and subsequent purification/assembly. Alternatively, the antibody molecules can be produced by expression of the components in a single host cell. Purification of bispecific antibody molecules can be performed by various methods such as affinity chromatography, e.g., using protein A and sequential pH elution. In other embodiments, affinity tags can be used for purification, e.g., histidine-containing tag, myc tag, or streptavidin tag.

In some embodiments, a method for generating bispecific antibodies disclosed herein comprises: generating a human antibody with a light chain of a lambda subtype; generating a human antibody with a light chain of kappa subtype; transfecting cells with DNA of both antibody arms; purifying the antibody with Protein A resin; confirming the presence of both lambda and kappa light chains with KappaSelect and LambdaFabSelect resin; analyzing the correct lambda and kappa heavy and light chain pairing by cleaving Fab arms with papain and running mass spectrometry. Experimental conditions for making and testing the multispecific molecules are provided in the Examples below.

Uses and Combination Therapies

Methods described herein include treating a cancer in a subject by using a multispecific molecule described herein, e.g., using a pharmaceutical composition described herein. Also provided are methods for reducing or ameliorating a symptom of a cancer in a subject, as well as methods for inhibiting the growth of a cancer and/or killing one or more cancer cells. In embodiments, the methods described herein decrease the size of a tumor and/or decrease the number of cancer cells in a subject administered with a described herein or a pharmaceutical composition described herein.

In embodiments, the cancer is a hematological cancer. In embodiments, the hematological cancer is a leukemia or a lymphoma. As used herein, a "hematologic cancer" refers to a tumor of the hematopoietic or lymphoid tissues, *e.g.,* a tumor that affects blood, bone marrow, or lymph nodes. Exemplary hematologic malignancies include, but are not limited to, leukemia (*e.g.,* acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic

lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), hairy cell leukemia, acute monocytic leukemia (AMoL), chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), or large granular lymphocytic leukemia), lymphoma (*e.g.,* AIDS-related lymphoma, cutaneous T-cell lymphoma, Hodgkin lymphoma (*e.g.,* classical Hodgkin lymphoma or nodular lymphocyte-predominant Hodgkin lymphoma), mycosis fungoides, non-Hodgkin lymphoma (*e.g.,* B-cell non-Hodgkin lymphoma (*e.g.,* Burkitt lymphoma, small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, or mantle cell lymphoma) or T-cell non-Hodgkin lymphoma (mycosis fungoides, anaplastic large cell lymphoma, or precursor T-lymphoblastic lymphoma)), primary central nervous system lymphoma, Sézary syndrome, Waldenström macroglobulinemia), chronic myeloproliferative neoplasm, Langerhans cell histiocytosis, multiple myeloma/plasma cell neoplasm, myelodysplastic syndrome, or myelodysplastic/myeloproliferative neoplasm.

In embodiments, the cancer is a solid cancer. Exemplary solid cancers include, but are not limited to, ovarian cancer, rectal cancer, stomach cancer, testicular cancer, cancer of the anal region, uterine cancer, colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, melanoma, Kaposi's sarcoma, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, brain stem glioma, pituitary adenoma, epidermoid cancer, carcinoma of the cervix squamous cell cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the vagina, sarcoma of soft tissue, cancer of the urethra, carcinoma of the vulva, cancer of the penis, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, spinal axis tumor, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, metastatic lesions of said cancers, or combinations thereof.

In embodiments, the multispecific molecules (or pharmaceutical composition) are administered in a manner appropriate to the disease to be treated or prevented. The quantity and frequency of administration will be determined by such factors as the condition of the patient, and the type and severity of the patient's disease. Appropriate dosages may be determined by clinical trials. For example, when "an effective amount" or "a therapeutic amount" is indicated,

the precise amount of the pharmaceutical composition (or multispecific molecules) to be administered can be determined by a physician with consideration of individual differences in tumor size, extent of infection or metastasis, age, weight, and condition of the subject. In embodiments, the pharmaceutical composition described herein can be administered at a dosage of 10^4 to 10^9 cells/kg body weight, e.g., 10^5 to 10^6 cells/kg body weight, including all integer values within those ranges. In embodiments, the pharmaceutical composition described herein can be administered multiple times at these dosages. In embodiments, the pharmaceutical composition described herein can be administered using infusion techniques described in immunotherapy (see, *e.g.*, Rosenberg et al., New Eng. J. of Med. 319:1676, 1988).

In embodiments, the multispecific molecules or pharmaceutical composition is administered to the subject parenterally. In embodiments, the cells are administered to the subject intravenously, subcutaneously, intratumorally, intranodally, intramuscularly, intradermally, or intraperitoneally. In embodiments, the cells are administered, e.g., injected, directly into a tumor or lymph node. In embodiments, the cells are administered as an infusion (e.g., as described in Rosenberg et al., New Eng. J. of Med. 319:1676, 1988) or an intravenous push. In embodiments, the cells are administered as an injectable depot formulation.
In embodiments, the subject is a mammal. In embodiments, the subject is a human, monkey, pig, dog, cat, cow, sheep, goat, rabbit, rat, or mouse. In embodimnets, the subject is a human. In embodiments, the subject is a pediatric subject, *e.g.*, less than 18 years of age, e.g., less than 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or less years of age. In embodiments, the subject is an adult, *e.g.*, at least 18 years of age, e.g., at least 19, 20, 21, 22, 23, 24, 25, 25-30, 30-35, 35-40, 40-50, 50-60, 60-70, 70-80, or 80-90 years of age.

Combination Therapies

The multispecific molecules disclosed herein can be used in combination with a second therapeutic agent or procedure.

In embodiments, the multispecific molecule and the second therapeutic agent or procedure are administered/performed after a subject has been diagnosed with a cancer, e.g., before the cancer has been eliminated from the subject. In embodiments, the multispecific molecule and the second therapeutic agent or procedure are administered/performed simultaneously or concurrently. For example, the delivery of one treatment is still occurring

when the delivery of the second commences, e.g., there is an overlap in administration of the treatments. In other embodiments, the multispecific molecule and the second therapeutic agent or procedure are administered/performed sequentially. For example, the delivery of one treatment ceases before the delivery of the other treatment begins.

In embodiments, combination therapy can lead to more effective treatment than monotherapy with either agent alone. In embodiments, the combination of the first and second treatment is more effective (e.g., leads to a greater reduction in symptoms and/or cancer cells) than the first or second treatment alone. In embodiments, the combination therapy permits use of a lower dose of the first or the second treatment compared to the dose of the first or second treatment normally required to achieve similar effects when administered as a monotherapy. In embodiments, the combination therapy has a partially additive effect, wholly additive effect, or greater than additive effect.

In one embodiment, the multispecific molecule is administered in combination with a therapy, *e.g.*, a cancer therapy (*e.g.*, one or more of anti-cancer agents, immunotherapy, photodynamic therapy (PDT), surgery and/or radiation). The terms "chemotherapeutic," "chemotherapeutic agent," and "anti-cancer agent" are used interchangeably herein. The administration of the multispecific molecule and the therapy, *e.g.*, the cancer therapy, can be sequential (with or without overlap) or simultaneous. Administration of the multispecific molecule can be continuous or intermittent during the course of therapy (*e.g.*, cancer therapy). Certain therapies described herein can be used to treat cancers and non-cancerous diseases. For example, PDT efficacy can be enhanced in cancerous and non-cancerous conditions (*e.g.*, tuberculosis) using the methods and compositions described herein (reviewed in, *e.g.*, Agostinis, P. *et al.* (2011) *CA Cancer J. Clin.* 61:250-281).

Anti-cancer therapies

In other embodiments, the multispecific molecule is administered in combination with a low or small molecular weight chemotherapeutic agent. Exemplary low or small molecular weight chemotherapeutic agents include, but not limited to, 13-cis-retinoic acid (isotretinoin, ACCUTANE®), 2-CdA (2-chlorodeoxyadenosine, cladribine, LEUSTATIN™), 5-azacitidine (azacitidine, VIDAZA®), 5-fluorouracil (5-FU, fluorouracil, ADRUCIL®), 6-mercaptopurine (6-MP, mercaptopurine, PURINETHOL®), 6-TG (6-thioguanine, thioguanine, THIOGUANINE

TABLOID®), abraxane (paclitaxel protein-bound), actinomycin-D (dactinomycin, COSMEGEN®), alitretinoin (PANRETIN®), all-transretinoic acid (ATRA, tretinoin, VESANOID®), altretamine (hexamethylmelamine, HMM, HEXALEN®), amethopterin (methotrexate, methotrexate sodium, MTX, TREXALL™, RHEUMATREX®), amifostine (ETHYOL®), arabinosylcytosine (Ara-C, cytarabine, CYTOSAR-U®), arsenic trioxide (TRISENOX®), asparaginase (Erwinia L-asparaginase, L-asparaginase, ELSPAR®, KIDROLASE®), BCNU (carmustine, BiCNU®), bendamustine (TREANDA®), bexarotene (TARGRETIN®), bleomycin (BLENOXANE®), busulfan (BUSULFEX®, MYLERAN®), calcium leucovorin (Citrovorum Factor, folinic acid, leucovorin), camptothecin-11 (CPT-11, irinotecan, CAMPTOSAR®), capecitabine (XELODA®), carboplatin (PARAPLATIN®), carmustine wafer (prolifeprospan 20 with carmustine implant, GLIADEL® wafer), CCI-779 (temsirolimus, TORISEL®), CCNU (lomustine, CeeNU), CDDP (cisplatin, PLATINOL®, PLATINOL-AQ®), chlorambucil (leukeran), cyclophosphamide (CYTOXAN®, NEOSAR®), dacarbazine (DIC, DTIC, imidazole carboxamide, DTIC-DOME®), daunomycin (daunorubicin, daunorubicin hydrochloride, rubidomycin hydrochloride, CERUBIDINE®), decitabine (DACOGEN®), dexrazoxane (ZINECARD®), DHAD (mitoxantrone, NOVANTRONE®), docetaxel (TAXOTERE®), doxorubicin (ADRIAMYCIN®, RUBEX®), epirubicin (ELLENCE™), estramustine (EMCYT®), etoposide (VP-16, etoposide phosphate, TOPOSAR®, VEPESID®, ETOPOPHOS®), floxuridine (FUDR®), fludarabine (FLUDARA®), fluorouracil (cream) (CARAC™, EFUDEX®, FLUOROPLEX®), gemcitabine (GEMZAR®), hydroxyurea (HYDREA®, DROXIA™, MYLOCEL™), idarubicin (IDAMYCIN®), ifosfamide (IFEX®), ixabepilone (IXEMPRA™), LCR (leurocristine, vincristine, VCR, ONCOVIN®, VINCASAR PFS®), L-PAM (L-sarcolysin, melphalan, phenylalanine mustard, ALKERAN®), mechlorethamine (mechlorethamine hydrochloride, mustine, nitrogen mustard, MUSTARGEN®), mesna (MESNEX™), mitomycin (mitomycin-C, MTC, MUTAMYCIN®), nelarabine (ARRANON®), oxaliplatin (ELOXATIN™), paclitaxel (TAXOL®, ONXAL™), pegaspargase (PEG-L-asparaginase, ONCOSPAR®), PEMETREXED (ALIMTA®), pentostatin (NIPENT®), procarbazine (MATULANE®), streptozocin (ZANOSAR®), temozolomide (TEMODAR®), teniposide (VM-26, VUMON®), TESPA (thiophosphoamide, thiotepa, TSPA, THIOPLEX®), topotecan (HYCAMTIN®), vinblastine

(vinblastine sulfate, vincaleukoblastine, VLB, ALKABAN-AQ®, VELBAN®), vinorelbine (vinorelbine tartrate, NAVELBINE®), and vorinostat (ZOLINZA®).

In another embodiment, the multispecific molecule is administered in conjunction with a biologic. Biologics useful in the treatment of cancers are known in the art and a binding molecule of the invention may be administered, for example, in conjunction with such known biologics. For example, the FDA has approved the following biologics for the treatment of breast cancer: HERCEPTIN® (trastuzumab, Genentech Inc., South San Francisco, Calif.; a humanized monoclonal antibody that has anti-tumor activity in HER2-positive breast cancer); FASLODEX® (fulvestrant, AstraZeneca Pharmaceuticals, LP, Wilmington, Del.; an estrogen-receptor antagonist used to treat breast cancer); ARIMIDEX® (anastrozole, AstraZeneca Pharmaceuticals, LP; a nonsteroidal aromatase inhibitor which blocks aromatase, an enzyme needed to make estrogen); Aromasin® (exemestane, Pfizer Inc., New York, N.Y.; an irreversible, steroidal aromatase inactivator used in the treatment of breast cancer); FEMARA® (letrozole, Novartis Pharmaceuticals, East Hanover, N.J.; a nonsteroidal aromatase inhibitor approved by the FDA to treat breast cancer); and NOLVADEX® (tamoxifen, AstraZeneca Pharmaceuticals, LP; a nonsteroidal antiestrogen approved by the FDA to treat breast cancer). Other biologics with which the binding molecules of the invention may be combined include: AVASTIN® (bevacizumab, Genentech Inc.; the first FDA-approved therapy designed to inhibit angiogenesis); and ZEVALIN® (ibritumomab tiuxetan, Biogen Idec, Cambridge, Mass.; a radiolabeled monoclonal antibody currently approved for the treatment of B-cell lymphomas).

In addition, the FDA has approved the following biologics for the treatment of colorectal cancer: AVASTIN®; ERBITUX® (cetuximab, ImClone Systems Inc., New York, N.Y., and Bristol-Myers Squibb, New York, N.Y.; is a monoclonal antibody directed against the epidermal growth factor receptor (EGFR)); GLEEVEC® (imatinib mesylate; a protein kinase inhibitor); and ERGAMISOL® (levamisole hydrochloride, Janssen Pharmaceutica Products, LP, Titusville, N.J.; an immunomodulator approved by the FDA in 1990 as an adjuvant treatment in combination with 5-fluorouracil after surgical resection in patients with Dukes' Stage C colon cancer).

For the treatment of lung cancer, exemplary biologics include TARCEVA® (erlotinib HCL, OSI Pharmaceuticals Inc., Melville, N.Y.; a small molecule designed to target the human epidermal growth factor receptor 1 (HER1) pathway).

For the treatment of multiple myeloma, exemplary biologics include VELCADE® Velcade (bortezomib, Millennium Pharmaceuticals, Cambridge Mass.; a proteasome inhibitor). Additional biologics include THALIDOMID® (thalidomide, Clegene Corporation, Warren, N.J.; an immunomodulatory agent and appears to have multiple actions, including the ability to inhibit the growth and survival of myeloma cells and anti-angiogenesis).

Additional exemplary cancer therapeutic antibodies include, but are not limited to, 3F8, abagovomab, adecatumumab, afutuzumab, alacizumab pegol, alemtuzumab (CAMPATH®, MABCAMPATH®), altumomab pentetate (HYBRI-CEAKER®), anatumomab mafenatox, anrukinzumab (IMA-638), apolizumab, arcitumomab (CEA-SCAN®), bavituximab, bectumomab (LYMPHOSCAN®), belimumab (BENLYSTA®, LYMPHOSTAT-B®), besilesomab (SCINTIMUN®), bevacizumab (AVASTIN®), bivatuzumab mertansine, blinatumomab, brentuximab vedotin, cantuzumab mertansine, capromab pendetide (PROSTASCINT®), catumaxomab (REMOVAB®), CC49, cetuximab (C225, ERBITUX®), citatuzumab bogatox, cixutumumab, clivatuzumab tetraxetan, conatumumab, dacetuzumab, denosumab (PROLIA®), detumomab, ecromeximab, edrecolomab (PANOREX®), elotuzumab, epitumomab cituxetan, epratuzumab, ertumaxomab (REXOMUN®), etaracizumab, farletuzumab, figitumumab, fresolimumab, galiximab, gemtuzumab ozogamicin (MYLOTARG®), girentuximab, glembatumumab vedotin, ibritumomab (ibritumomab tiuxetan, ZEVALIN®), igovomab (INDIMACIS-125®), intetumumab, inotuzumab ozogamicin, ipilimumab, iratumumab, labetuzumab (CEA-CIDE®), lexatumumab, lintuzumab, lucatumumab, lumiliximab, mapatumumab, matuzumab, milatuzumab, minretumomab, mitumomab, nacolomab tafenatox, naptumomab estafenatox, necitumumab, nimotuzumab (THERACIM®, THERALOC®), nofetumomab merpentan (VERLUMA®), ofatumumab (ARZERRA®), olaratumab, oportuzumab monatox, oregovomab (OVAREX®), panitumumab (VECTIBIX®), pemtumomab (THERAGYN®), pertuzumab (OMNITARG®), pintumomab, pritumumab, ramucirumab, ranibizumab (LUCENTIS®), rilotumumab, rituximab (MABTHERA®, RITUXAN®), robatumumab, satumomab pendetide, sibrotuzumab, siltuximab, sontuzumab, tacatuzumab tetraxetan (AFP-CIDE®), taplitumomab paptox, tenatumomab, TGN1412, ticilimumab (tremelimumab), tigatuzumab, TNX-650, tositumomab (BEXXAR®), trastuzumab (HERCEPTIN®), tremelimumab, tucotuzumab celmoleukin,

veltuzumab, volociximab, votumumab (HUMASPECT®), zalutumumab (HUMAX-EGFR®), and zanolimumab (HUMAX-CD4®).

In other embodiments, the multispecific molecule is administered in combination with a viral cancer therapeutic agent. Exemplary viral cancer therapeutic agents include, but not limited to, vaccinia virus (vvDD-CDSR), carcinoembryonic antigen-expressing measles virus, recombinant vaccinia virus (TK-deletion plus GM-CSF), Seneca Valley virus-001, Newcastle virus, coxsackie virus A21, GL-ONC1, EBNA1 C-terminal/LMP2 chimeric protein-expressing recombinant modified vaccinia Ankara vaccine, carcinoembryonic antigen-expressing measles virus, G207 oncolytic virus, modified vaccinia virus Ankara vaccine expressing p53, OncoVEX GM-CSF modified herpes-simplex 1 virus, fowlpox virus vaccine vector, recombinant vaccinia prostate-specific antigen vaccine, human papillomavirus 16/18 L1 virus-like particle/AS04 vaccine, MVA-EBNA1/LMP2 Inj. vaccine, quadrivalent HPV vaccine, quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine (GARDASIL®), recombinant fowlpox-CEA(6D)/TRICOM vaccine; recombinant vaccinia-CEA(6D)-TRICOM vaccine, recombinant modified vaccinia Ankara-5T4 vaccine, recombinant fowlpox-TRICOM vaccine, oncolytic herpes virus NV1020, HPV L1 VLP vaccine V504, human papillomavirus bivalent (types 16 and 18) vaccine (CERVARIX®), herpes simplex virus HF10, Ad5CMV-p53 gene, recombinant vaccinia DF3/MUC1 vaccine, recombinant vaccinia-MUC-1 vaccine, recombinant vaccinia-TRICOM vaccine, ALVAC MART-1 vaccine, replication-defective herpes simplex virus type I (HSV-1) vector expressing human Preproenkephalin (NP2), wild-type reovirus, reovirus type 3 Dearing (REOLYSIN®), oncolytic virus HSV1716, recombinant modified vaccinia Ankara (MVA)-based vaccine encoding Epstein-Barr virus target antigens, recombinant fowlpox-prostate specific antigen vaccine, recombinant vaccinia prostate-specific antigen vaccine, recombinant vaccinia-B7.1 vaccine, rAd-p53 gene, Ad5-delta24RGD, HPV vaccine 580299, JX-594 (thymidine kinase-deleted vaccinia virus plus GM-CSF), HPV-16/18 L1/AS04, fowlpox virus vaccine vector, vaccinia-tyrosinase vaccine, MEDI-517 HPV-16/18 VLP AS04 vaccine, adenoviral vector containing the thymidine kinase of herpes simplex virus TK99UN, HspE7, FP253/Fludarabine, ALVAC(2) melanoma multi-antigen therapeutic vaccine, ALVAC-hB7.1, canarypox-hIL-12 melanoma vaccine, Ad-REIC/Dkk-3, rAd-IFN SCH 721015, TIL-Ad-INFg, Ad-ISF35, and coxsackievirus A21 (CVA21, CAVATAK®).

In other embodiments, the multispecific molecule is administered in combination with a nanopharmaceutical. Exemplary cancer nanopharmaceuticals include, but not limited to, ABRAXANE® (paclitaxel bound albumin nanoparticles), CRLX101 (CPT conjugated to a linear cyclodextrin-based polymer), CRLX288 (conjugating docetaxel to the biodegradable polymer poly (lactic-co-glycolic acid)), cytarabine liposomal (liposomal Ara-C, DEPOCYT™), daunorubicin liposomal (DAUNOXOME®), doxorubicin liposomal (DOXIL®, CAELYX®), encapsulated-daunorubicin citrate liposome (DAUNOXOME®), and PEG anti-VEGF aptamer (MACUGEN®).

In some embodiments, the multispecific molecule is administered in combination with paclitaxel or a paclitaxel formulation, e.g., TAXOL®, protein-bound paclitaxel (e.g., ABRAXANE®). Exemplary paclitaxel formulations include, but are not limited to, nanoparticle albumin-bound paclitaxel (ABRAXANE®, marketed by Abraxis Bioscience), docosahexaenoic acid bound-paclitaxel (DHA-paclitaxel, Taxoprexin, marketed by Protarga), polyglutamate bound-paclitaxel (PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX, marketed by Cell Therapeutic), the tumor-activated prodrug (TAP), ANG105 (Angiopep-2 bound to three molecules of paclitaxel, marketed by ImmunoGen), paclitaxel-EC-1 (paclitaxel bound to the erbB2-recognizing peptide EC-1; see Li *et al., Biopolymers* (2007) 87:225-230), and glucose-conjugated paclitaxel (*e.g.,* 2'-paclitaxel methyl 2-glucopyranosyl succinate, see Liu *et al., Bioorganic & Medicinal Chemistry Letters* (2007) 17:617-620).

Exemplary RNAi and antisense RNA agents for treating cancer include, but not limited to, CALAA-01, siG12D LODER (Local Drug EluteR), and ALN-VSP02.

Other cancer therapeutic agents include, but not limited to, cytokines (e.g., aldesleukin (IL-2, Interleukin-2, PROLEUKIN®), alpha Interferon (IFN-alpha, Interferon alfa, INTRON® A (Interferon alfa-2b), ROFERON-A® (Interferon alfa-2a)), Epoetin alfa (PROCRIT®), filgrastim (G-CSF, Granulocyte - Colony Stimulating Factor, NEUPOGEN®), GM-CSF (Granulocyte Macrophage Colony Stimulating Factor, sargramostim, LEUKINE™), IL-11 (Interleukin-11, oprelvekin, NEUMEGA®), Interferon alfa-2b (PEG conjugate) (PEG interferon, PEG-INTRON™), and pegfilgrastim (NEULASTA™)), hormone therapy agents (e.g., aminoglutethimide (CYTADREN®), anastrozole (ARIMIDEX®), bicalutamide (CASODEX®), exemestane (AROMASIN®), fluoxymesterone (HALOTESTIN®), flutamide (EULEXIN®), fulvestrant (FASLODEX®), goserelin (ZOLADEX®), letrozole (FEMARA®), leuprolide

(ELIGARD™, LUPRON®, LUPRON DEPOT®, VIADUR™), megestrol (megestrol acetate, MEGACE®), nilutamide (ANANDRON®, NILANDRON®), octreotide (octreotide acetate, SANDOSTATIN®, SANDOSTATIN LAR®), raloxifene (EVISTA®), romiplostim (NPLATE®), tamoxifen (NOVALDEX®), and toremifene (FARESTON®)), phospholipase A2 inhibitors (e.g., anagrelide (AGRYLIN®)), biologic response modifiers (e.g., BCG (THERACYS®, TICE®), and Darbepoetin alfa (ARANESP®)), target therapy agents (e.g., bortezomib (VELCADE®), dasatinib (SPRYCEL™), denileukin diftitox (ONTAK®), erlotinib (TARCEVA®), everolimus (AFINITOR®), gefitinib (IRESSA®), imatinib mesylate (STI-571, GLEEVEC™), lapatinib (TYKERB®), sorafenib (NEXAVAR®), and SU11248 (sunitinib, SUTENT®)), immunomodulatory and antiangiogenic agents (e.g., CC-5013 (lenalidomide, REVLIMID®), and thalidomide (THALOMID®)), glucocorticosteroids (e.g., cortisone (hydrocortisone, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, ALA-CORT®, HYDROCORT ACETATE®, hydrocortone phosphate LANACORT®, SOLU-CORTEF®), decadron (dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, DEXASONE®, DIODEX®, HEXADROL®, MAXIDEX®), methylprednisolone (6-methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, DURALONE®, MEDRALONE®, MEDROL®, M-PREDNISOL®, SOLU-MEDROL®), prednisolone (DELTA-CORTEF®, ORAPRED®, PEDIAPRED®, PRELONE®), and prednisone (DELTASONE®, LIQUID PRED®, METICORTEN®, ORASONE®)), and bisphosphonates (e.g., pamidronate (AREDIA®), and zoledronic acid (ZOMETA®))

In some embodiments, the multispecific molecule is used in combination with a tyrosine kinase inhibitor (*e.g.*, a receptor tyrosine kinase (RTK) inhibitor). Exemplary tyrosine kinase inhibitor include, but are not limited to, an epidermal growth factor (EGF) pathway inhibitor (*e.g.*, an epidermal growth factor receptor (EGFR) inhibitor), a vascular endothelial growth factor (VEGF) pathway inhibitor (*e.g.*, an antibody against VEGF, a VEGF trap, a vascular endothelial growth factor receptor (VEGFR) inhibitor (*e.g.*, a VEGFR-1 inhibitor, a VEGFR-2 inhibitor, a VEGFR-3 inhibitor)), a platelet derived growth factor (PDGF) pathway inhibitor (*e.g.*, a platelet derived growth factor receptor (PDGFR) inhibitor (*e.g.*, a PDGFR-ß inhibitor)), a RAF-1 inhibitor, a KIT inhibitor and a RET inhibitor. In some embodiments, the anti-cancer agent used in combination with the AHCM agent is selected from the group consisting of: axitinib (AG013736), bosutinib (SKI-606), cediranib (RECENTIN™, AZD2171), dasatinib

(SPRYCEL®, BMS-354825), erlotinib (TARCEVA®), gefitinib (IRESSA®), imatinib (Gleevec®, CGP57148B, STI-571), lapatinib (TYKERB®, TYVERB®), lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib (TASIGNA®), semaxanib (semaxinib, SU5416), sunitinib (SUTENT®, SU11248), toceranib (PALLADIA®), vandetanib (ZACTIMA®, ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab (HERCEPTIN®), bevacizumab (AVASTIN®), rituximab (RITUXAN®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), ranibizumab (Lucentis®), nilotinib (TASIGNA®), sorafenib (NEXAVAR®), alemtuzumab (CAMPATH®), gemtuzumab ozogamicin (MYLOTARG®), ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992 (TOVOK™), SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120 (VARGATEF®), AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, XL228, AEE788, AG-490, AST-6, BMS-599626, CUDC-101, PD153035, pelitinib (EKB-569), vandetanib (zactima), WZ3146, WZ4002, WZ8040, ABT-869 (linifanib), AEE788, AP24534 (ponatinib), AV-951(tivozanib), axitinib, BAY 73-4506 (regorafenib), brivanib alaninate (BMS-582664), brivanib (BMS-540215), cediranib (AZD2171), CHIR-258 (dovitinib), CP 673451, CYC116, E7080, Ki8751, masitinib (AB1010), MGCD-265, motesanib diphosphate (AMG-706), MP-470, OSI-930, Pazopanib Hydrochloride, PD173074,nSorafenib Tosylate(Bay 43-9006), SU 5402, TSU-68(SU6668), vatalanib, XL880 (GSK1363089, EXEL-2880). Selected tyrosine kinase inhibitors are chosen from sunitinib, erlotinib, gefitinib, or sorafenib. In one embodiment, the tyrosine kinase inhibitor is sunitinib.

In one embodiment, the multispecific molecule is administered in combination with one of more of: an anti-angiogenic agent, or a vascular targeting agent or a vascular disrupting agent. Exemplary anti-angiogenic agents include, but are not limited to, VEGF inhibitors (*e.g.*, anti-VEGF antibodies (*e.g.*, bevacizumab); VEGF receptor inhibitors (*e.g.*, itraconazole); inhibitors of cell proliferatin and/or migration of endothelial cells (*e.g.*, carboxyamidotriazole, TNP-470); inhibitors of angiogenesis stimulators (*e.g.*, suramin), among others. A vascular-targeting agent (VTA) or vascular disrupting agent (VDA) is designed to damage the vasculature (blood vessels) of cancer tumors causing central necrosis (reviewed in, *e.g.*, Thorpe, P.E. (2004) *Clin. Cancer Res.* Vol. 10:415-427). VTAs can be small-molecule. Exemplary small-molecule VTAs include, but are not limited to, microtubule destabilizing drugs (e.g., combretastatin A-4 disodium phosphate (CA4P), ZD6126, AVE8062, Oxi 4503); and vadimezan (ASA404).

Immune checkpoint inhibitors

In other embodiments, methods described herein comprise use of an immune checkpoint inhibitor in combination with the multispecific molecule. The methods can be used in a therapeutic protocol *in vivo*.

In embodiments, an immune checkpoint inhibitor inhibits a checkpoint molecule. Exemplary checkpoint molecules include but are not limited to CTLA4, PD1, PD-L1, PD-L2, TIM3, LAG3, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), BTLA, KIR, MHC class I, MHC class II, GAL9, VISTA, BTLA, TIGIT, LAIR1, and A2aR. See, e.g., Pardoll. Nat. Rev. Cancer 12.4(2012):252-64, incorporated herein by reference.

In embodiments, the immune checkpoint inhibitor is a PD-1 inhibitor, e.g., an anti-PD-1 antibody such as Nivolumab, Pembrolizumab or Pidilizumab. Nivolumab (also called MDX-1106, MDX-1106-04, ONO-4538, or BMS-936558) is a fully human IgG4 monoclonal antibody that specifically inhibits PD1. See, e.g., US 8,008,449 and WO2006/121168. Pembrolizumab (also called Lambrolizumab, MK-3475, MK03475, SCH-900475 or KEYTRUDA®; Merck) is a humanized IgG4 monoclonal antibody that binds to PD-1. See, e.g., Hamid, O. *et al.* (2013) *New England Journal of Medicine* 369 (2): 134–44, US 8,354,509 and WO2009/114335. Pidilizumab (also called CT-011 or Cure Tech) is a humanized IgG1k monoclonal antibody that binds to PD1. See, e.g., WO2009/101611. In one embodiment, the inhibitor of PD-1 is an antibody molecule having a sequence substantially identical or similar thereto, *e.g.*, a sequence at least 85%, 90%, 95% identical or higher to the sequence of Nivolumab, Pembrolizumab or Pidilizumab. Additional anti-PD1 antibodies, e.g., AMP 514 (Amplimmune), are described, e.g., in US 8,609,089, US 2010028330, and/or US 20120114649.

In some embodiments, the PD-1 inhibitor is an immunoadhesin, e.g., an immunoadhesin comprising an extracellular/PD-1 binding portion of a PD-1 ligand (e.g., PD-L1 or PD-L2) that is fused to a constant region (*e.g.*, an Fc region of an immunoglobulin). In embodiments, the PD-1 inhibitor is AMP-224 (B7-DCIg, *e.g.*, described in WO2011/066342and WO2010/027827), a PD-L2 Fc fusion soluble receptor that blocks the interaction between B7-H1 and PD-1.

In embodiments, the immune checkpoint inhibitor is a PD-L1 inhibitor, e.g., an antibody molecule. In some embodiments, the PD-L1 inhibitor is YW243.55.S70, MPDL3280A, MEDI-

4736, MSB-0010718C, or MDX-1105. In some embodiments, the anti-PD-L1 antibody is MSB0010718C (also called A09-246-2; Merck Serono), which is a monoclonal antibody that binds to PD-L1. Exemplary humanized anti-PD-L1 antibodies are described, e.g., in WO2013/079174. In one embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody, e.g., YW243.55.S70. The YW243.55.S70 antibody is described, e.g., in WO 2010/077634. In one embodiment, the PD-L1 inhibitor is MDX-1105 (also called BMS-936559), which is described, e.g., in WO2007/005874. In one embodiment, the PD-L1 inhibitor is MDPL3280A (Genentech / Roche), which is a human Fc-optimized IgG1 monoclonal antibody against PD-L1. See, e.g., U.S. Patent No.: 7,943,743 and U.S Publication No.: 20120039906. In one embodiment, the inhibitor of PD-L1 is an antibody molecule having a sequence substantially identical or similar thereto, *e.g.*, a sequence at least 85%, 90%, 95% identical or higher to the sequence of YW243.55.S70, MPDL3280A, MEDI-4736, MSB-0010718C, or MDX-1105.

In embodiments, the immune checkpoint inhibitor is a PD-L2 inhibitor, e.g., AMP-224 (which is a PD-L2 Fc fusion soluble receptor that blocks the interaction between PD1 and B7-H1. See, e.g., WO2010/027827 and WO2011/066342.

In one embodiment, the immune checkpoint inhibitor is a LAG-3 inhibitor, e.g., an anti LAG-3 antibody molecule. In embodiments, the anti-LAG-3 antibody is BMS-986016 (also called BMS986016; Bristol-Myers Squibb). BMS-986016 and other humanized anti-LAG-3 antibodies are described, e.g., in US 2011/0150892, WO2010/019570, and WO2014/008218.

In embodiments, the immune checkpoint inhibitor is a TIM-3 inhibitor, e.g., anti-TIM3 antibody molecule, e.g., described in U.S. Patent No.: 8,552,156, WO 2011/155607, EP 2581113 and U.S Publication No.: 2014/044728.

In embodiments, the immune checkpoint inhibitor is a CTLA-4 inhibitor, e.g., anti-CTLA-4 antibody molecule. Exemplary anti-CTLA4 antibodies include Tremelimumab (IgG2 monoclonal antibody from Pfizer, formerly known as ticilimumab, CP-675,206); and Ipilimumab (also called MDX-010, CAS No. 477202-00-9). Other exemplary anti-CTLA-4 antibodies are described, *e.g.,* in U.S. Pat. No. 5,811,097.

EXAMPLES

The following examples are intended to be illustrative, and are not meant in any way to be limiting.

Methods

1. Construction of the plasmids of NanoBiT constructs.

The DNA encoding the protein sequences was optimized for expression in *Cricetulus griseus*, synthesized, and cloned into the pcDNA3.4-TOPO (Life Technologies A14697) using Gateway cloning. The nucleic acid sequences used are shown in Table 1.

Table 1. Nucleic acid sequences of ORFs.

SEQ ID NO	Description	Nucleic Acid Sequence
SEQ ID NO: 1	α-amyloid β heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGCTGGTTGAATCTGGTGGCGGAGTGGTGCAGCCTGG CAGATCTCTGAGACTGTCTTGTGCCGCCTCTGGCTTCGCCTTCTCTTCTTAC GGCATGCACTGGGTCCGACAGGCCCCTGGAAAAGGACTGGAATGGGTCGCCG TGATTTGGTTCGACGGCACCAAGAAGTACTACACCGACTCCGTGAAGGGCAG ATTCACCATCAGCCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAT ACCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTGCCAGAGATAGAGGCA TCGGCGCTCGGAGAGGCCCTTACTATATGGATGTGTGGGGCAAGGGCACCAC CGTGACAGTGTCCTCTGCTTCTACCAAGGGACCCAGCGTTTTCCCTCTGGCT CCATCCTCTAAGTCCACCTCTGGTGGAACCGCTGCTCTGGGCTGTCTGGTCA AGGATTACTTCCCTGAGCCTGTGACCGTGTCCTGGAACTCTGGTGCTCTGAC ATCCGGCGTGCACACCTTTCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCT CTGTCCTCTGTCGTGACCGTGCCTTCTAGCTCTCTGGGCACCCAGACCTACA TCTGCAACGTGAACCACAAGCCTTCCAACACCAAAGTGGACAAGAGAGTGGA ACCCAAGTCCTGCGGATCTTCTGGCGGCGGAGGAAGCGGAGGCGGAGGATCT AGCGGCGGAGTGTTCACCCTGGAAGATTTCGTCGGCGATTGGGAGCAGACCG CCGCCTATAATCTGGACCAGGTTCTGGAACAAGGCGGCGTGTCCTCTCTGCT GCAGAATCTGGCTGTGTCTGTGACCCCTATCCAGAGAATCGTGCGCTCTGGC GAGAACGCCCTGAAGATCGACATCCACGTGATCATCCCTTACGAGGGCCTGT CTGCCGATCAGATGGCTCAGATCGAAGAGGTGTTCAAGGTGGTGTACCCCGT GGACGACCACCACTTCAAAGTGATCCTGCCTTACGGCACCCTGGTCATCGAT GGCGTGACCCCAAACATGCTGAACTACTTCGGCAGACCCTACGAGGGAATCG CCGTGTTCGATGGCAAGAAAATCACCGTGACCGGCACACTGTGGAACGGCAA CAAGATCATCGACGAGCGGCTGATCACCCCTGACGGCTCTATGCTGTTCAGA GTGACCATCAACTCCTAATGA
SEQ ID NO: 2	α-amyloid β light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGCGACATCCAGATGACCCAGTCTCCATCCTCTCTGTCTGCCTCTGT GGGCGACAGAGTGACCATCACCTGTAGAGCCAGCCAGTCCATCTCCTCCTAC CTGAACTGGTATCAGCAGAAGCCTGGCAAGGCTCCCAAGCTGCTGATCTACG CTGCTAGCTCTCTGCAGTCTGGCGTGCCCTCTAGATTTTCCGGCTCTGGCTC TGGCACCGACTTCACCCTGACAATCAGTTCCCTGCAGCCTGAGGACTTCGCC ACCTACTACTGCCAGCAGTCCTACAGCACACCCTTGACCTTTGGCGGAGGCA CCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC

		ACCATCCGACGAACAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACTC TACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCGTGA CCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGGTGGCGGAGGAAGCGG AGGCGGAGGATCATCTGGCGGAGTGACCGGCTACAGACTGTTCGAAGAGATC CTGTAATGA
SEQ ID NO: 3	α-amyloid β light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGCGACATCCAGATGACCCAGTCTCCATCCTCTCTGTCTGCCTCTGT GGGCGACAGAGTGACCATCACCTGTAGAGCCAGCCAGTCCATCTCCTCCTAC CTGAACTGGTATCAGCAGAAGCCTGGCAAGGCTCCCAAGCTGCTGATCTACG CTGCTAGCTCTCTGCAGTCTGGCGTGCCCTCTAGATTTTCCGGCTCTGGCTC TGGCACCGACTTCACCCTGACAATCAGTTCCCTGCAGCCTGAGGACTTCGCC ACCTACTACTGCCAGCAGTCCTACAGCACACCCTTGACCTTTGGCGGAGGCA CCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCATCCGACGAACAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACTC TACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCGTGA CCAAGTCTTTCAACAGAGGCGAGTGCTAATGA
SEQ ID NO: 4	α-Clostridium difficile toxin B heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAAGTGCAGTTGGTGCAGTCTGGCGCCGAAGTGAAGAAGTCCGG CGAGTCCCTGAAGATCTCCTGCAAAGGCTCCGGCTACTCCTTCACCTCTTAC TGGATCGGCTGGGTCCGACAGATGCCTGGCAAAGGACTGGAATGGATGGGCA TCTTCTACCCCGGCGACTCCTCTACCAGATACTCCCCTAGCTTTCAGGGCCA AGTGACCATCTCCGCCGACAAGTCTGTGAACACCGCCTACCTGCAGTGGTCC TCTCTGAAGGCCTCTGACACCGCCATGTACTACTGCGCCAGAAGAAGAAACT GGGGCAACGCCTTCGATATCTGGGGCCAGGGAACAATGGTCACCGTGTCCTC TGCTTCCACCAAGGGACCTTCCGTGTTTCCTCTGGCTCCTTCCAGCAAGTCT ACCTCTGGTGGAACCGCTGCTCTGGGCTGCCTGGTCAAGGATTACTTTCCTG AGCCTGTGACCGTGTCTTGGAACTCTGGTGCTCTGACCTCCGGCGTGCACAC ATTTCCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTG ACCGTGCCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACC ACAAGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCTTGCGG ATCTTCCGGTGGCGGAGGATCTGGCGGAGGTGGAAGTAGTGGCGGAGTGTTC ACCCTGGAAGATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATAATCTGG ACCAGGTTCTGGAACAAGGCGGCGTCAGCTCTCTGCTGCAGAATCTGGCTGT GTCTGTGACCCCTATCCAGAGAATCGTGCGCTCTGGCGAGAACGCTCTGAAG ATCGACATCCACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATCAGATGG CTCAGATCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTT CAAAGTGATCCTGCCTTACGGCACCCTGGTCATCGATGGCGTGACCCCAAAC ATGCTGAACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCA AGAAAATCACCGTGACCGGCACACTGTGGAACGGCAACAAGATCATCGACGA GCGGCTGATCACCCCTGACGGCTCTATGCTGTTCCGCGTGACCATCAACTCC TAATGA
SEQ ID NO: 5	α-Clostridium difficile toxin B light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGGCACATTGTCTCTGAGTCC TGGCGAGAGAGCTACCCTGTCTTGCAGAGCTTCCCAGTCCGTGTCCTCTTCC TACCTGGCCTGGTATCAGCAGAAGCCTGGACAGGCTCCCAGACTGCTGATCT

	- SmBiT	ACGGCGCCTCTTCTAGAGCCACAGGCATCCCTGACAGATTCTCCGGCTCTGG CTCTGGCACCGACTTCACCCTGACCATCTCTAGACTGGAACCCGAGGACTTC GCCGTGTACTACTGCCAGCAGTATGGCTCCTCTACCTGGACCTTTGGACAGG GCACCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTT CCCACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTG CTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATG CCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGA CTCTACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCG TGACCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGGTGGCGGAGGATC TGGCGGAGGCGGATCTAGTGGCGGAGTGACCGGCTACAGACTGTTCGAAGAG ATCCTGTAATGA
SEQ ID NO: 6	α-Clostridium difficile toxin B light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGGCACATTGTCTCTGAGTCC TGGCGAGAGAGCTACCCTGTCTTGCAGAGCTTCCCAGTCCGTGTCCTCTTCC TACCTGGCCTGGTATCAGCAGAAGCCTGGACAGGCTCCCAGACTGCTGATCT ACGGCGCCTCTTCTAGAGCCACAGGCATCCCTGACAGATTCTCCGGCTCTGG CTCTGGCACCGACTTCACCCTGACCATCTCTAGACTGGAACCCGAGGACTTC GCCGTGTACTACTGCCAGCAGTATGGCTCCTCTACCTGGACCTTTGGACAGG GCACCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTT CCCACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTG CTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATG CCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGA CTCTACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCG TGACCAAGTCTTTCAACAGAGGCGAGTGCTAATGA
SEQ ID NO: 7	α-connective tissue growth factor heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAAGGCCAGTTGGTTCAGTCTGGCGGAGGACTTGTTCACCCTGG CGGATCTCTGAGACTGTCTTGTGCTGGCTCTGGCTTCACCTTCTCCAGCTAC GGCATGCACTGGGTTCGACAGGCCCCTGGAAAAGGACTGGAATGGGTGTCCG GAATCGGCACCGGCGGAGGCACCTATTCTACCGATTCTGTGAAGGGCAGATT CACCATCAGCCGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAACAGC CTGAGAGCCGAGGACATGGCCGTGTACTACTGTGCCAGAGGCGATTACTACG GCTCCGGCTCTTTCTTCGACTGTTGGGGACAGGGCACACTGGTCACCGTGTC CTCTGCTTCTACCAAGGGACCCTCTGTGTTCCCTCTGGCTCCTTCCAGCAAG TCTACCTCTGGTGGAACCGCTGCTCTGGGCTGCCTGGTCAAGGATTACTTTC CTGAGCCTGTGACCGTGTCTTGGAACTCTGGTGCTCTGACCTCCGGCGTGCA CACATTTCCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTC GTGACCGTGCCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGA ACCACAAGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCTTG CGGATCTTCTGGCGGCGGAGGAAGCGGAGGCGGAGGATCTAGTGGCGGAGTG TTTACCCTGGAAGATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATAATC TGGACCAGGTTCTGGAACAAGGCGGCGTCAGCTCTCTGCTGCAGAATCTGGC TGTGTCTGTGACCCCTATCCAGAGAATCGTGCGCTCTGGCGAGAACGCCCTG AAGATCGACATCCACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATCAGA TGGCTCAGATCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCA CTTCAAAGTGATCCTGCCTTACGGCACCCTGGTCATCGATGGCGTGACCCCA AACATGCTGAACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACG GCAAGAAAATCACCGTGACCGGCACACTGTGGAACGGCAACAAGATCATCGA CGAGCGGCTGATCACCCCTGACGGCTCCATGCTGTTTAGAGTGACCATCAAC TCCTAATGA

SEQ ID NO: 8	α-connective tissue growth factor light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGCGACATCCAGATGACCCAGTCTCCATCCTCTCTGTCTGCCTCTGT GGGCGACAGAGTGACCATCACCTGTAGAGCCTCTCAGGGCATCTCTAGCTGG CTGGCCTGGTATCAGCAGAAGCCTGAGAAGGCCCCTAAGAGCCTGATCTACG CTGCCAGTTCTCTGCAGTCTGGCGTGCCCTCTAGATTCTCTGGCTCTGGATC TGGCACCGACTTCACCCTGACAATCTCTAGCCTGCAGCCTGAGGACTTCGCC ACCTACTACTGCCAGCAGTACAACAGCTACCCTCCTACCTTTGGCCAGGGCA CCAAGCTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACTC TACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCGTGA CCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGGTGGCGGAGGATCTGG CGGAGGTGGAAGTAGTGGCGGCGTGACCGGCTACAGACTGTTCGAAGAGATC CTGTAATGA
SEQ ID NO: 9	α-connective tissue growth factor light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGCGACATCCAGATGACCCAGTCTCCATCCTCTCTGTCTGCCTCTGT GGGCGACAGAGTGACCATCACCTGTAGAGCCTCTCAGGGCATCTCTAGCTGG CTGGCCTGGTATCAGCAGAAGCCTGAGAAGGCCCCTAAGAGCCTGATCTACG CTGCCAGTTCTCTGCAGTCTGGCGTGCCCTCTAGATTCTCTGGCTCTGGATC TGGCACCGACTTCACCCTGACAATCTCTAGCCTGCAGCCTGAGGACTTCGCC ACCTACTACTGCCAGCAGTACAACAGCTACCCTCCTACCTTTGGCCAGGGCA CCAAGCTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACTC TACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCGTGA CCAAGTCTTTCAACAGAGGCGAGTGCTAATGA
SEQ ID NO: 10	α-CSF2 heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGTTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCTGG CGCTTCTGTGAAGGTGTCCTGCAAGGCCTCTGGCTACTCCTTCACCAACTAC TACATCCACTGGGTCCGACAGGCCCCTGGACAGAGATTGGAGTGGATGGGCT GGATCAACGCCGGCAACGGCAACACCAAGTACTCCCAGAAATTCCAGGGCAG AGTGACCATCACCAGAGACACCTCTGCCTCCACCGCCTACATGGAACTGTCC AGCCTGAGATCTGAGGACACCGCCGTGTACTACTGCGTGCGGAGACAGCGGT TCCCCTACTACTTTGATTATTGGGGCCAGGGCACCCTGGTCACCGTGTCCTC TGCTTCTACAAAGGGCCCCTCTGTGTTCCCTCTGGCTCCTTCCTCTAAATCC ACCTCTGGCGGAACAGCTGCTCTGGGCTGTCTGGTCAAGGACTACTTTCCTG AGCCTGTGACCGTGTCTTGGAACTCTGGTGCTCTGACATCCGGCGTGCACAC CTTTCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCCTCTGTCGTG ACCGTGCCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACC ACAAGCCTTCTAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCTTGCGG ATCTTCTGGTGGCGGAGGATCTGGCGGAGGCGGATCTAGTGGCGGAGTGTTC ACCCTGGAAGATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATAATCTGG ACCAGGTTCTGGAACAAGGCGGGGTGTCCTCTCTGCTGCAGAATCTGGCTGT GTCTGTGACCCCTATCCAGAGAATCGTGCGCTCTGGCGAGAACGCCCTGAAG ATCGACATCCACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATCAGATGG CTCAGATCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTT CAAAGTGATCCTGCCTTACGGCACCCTCGTGATCGATGGCGTGACCCCAAAC

		ATGCTGAACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCA AGAAAATCACCGTGACCGGCACACTGTGGAACGGAAACAAGATCATCGACGA GCGGCTGATCACCCCTGACGGCTCTATGCTGTTTAGAGTGACAATCAACTCC TAATGA
SEQ ID NO: 11	α-CSF2 light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGCCACATTGTCTGTGTCTCC CGGCGAGAGAGCTACCCTGTCTTGTAGAGCTTCTCAGTCCGTGGGCACCAAC GTGGCCTGGTATCAGCAGAAACCTGGACAGGCCCCTCGGGTGCTGATCTACT CTACCTCTTCTAGAGCCACCGGCATCACCGACAGATTCTCTGGCTCTGGATC TGGCACCGACTTCACCCTGACCATCTCCAGACTGGAACCTGAGGACTTCGCC GTGTACTACTGCCAGCAGTTCAACAAGTCCCCTCTGACCTTTGGCGGAGGCA CCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACTC TACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCGTGA CCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGGTGGCGGAGGAAGCGG AGGCGGAGGATCATCTGGCGGAGTGACCGGCTACAGACTGTTCGAAGAGATC CTGTAATGA
SEQ ID NO: 12	α-CSF2 light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGCCACATTGTCTGTGTCTCC CGGCGAGAGAGCTACCCTGTCTTGTAGAGCTTCTCAGTCCGTGGGCACCAAC GTGGCCTGGTATCAGCAGAAACCTGGACAGGCCCCTCGGGTGCTGATCTACT CTACCTCTTCTAGAGCCACCGGCATCACCGACAGATTCTCTGGCTCTGGATC TGGCACCGACTTCACCCTGACCATCTCCAGACTGGAACCTGAGGACTTCGCC GTGTACTACTGCCAGCAGTTCAACAAGTCCCCTCTGACCTTTGGCGGAGGCA CCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACTC TACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCGTGA CCAAGTCTTTCAACAGAGGCGAGTGCTAATGA
SEQ ID NO: 13	α-CTLA4 heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGCTGGTGGAATCTGGTGGCGGAGTTGTGCAGCCTGG CAGATCCCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCAGCTAC ACCATGCACTGGGTCCGACAGGCCCCTGGCAAAGGATTGGAGTGGGTCACCT TCATCTCTTACGACGGCAACAACAAGTACTACGCCGACTCCGTGAAGGGCAG ATTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGAGAGCCGAGGACACCGCCATCTACTACTGTGCTAGAACCGGCTGGC TGGGCCCCTTTGATTATTGGGGACAGGGCACCCTGGTCACCGTGTCCTCTGC TTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACC TCTGGCGGAACAGCTGCTCTGGGCTGCCTGGTCAAGGACTACTTTCCTGAGC CTGTGACCGTGTCTTGGAACTCTGGCGCTCTGACATCCGGCGTGCACACATT TCCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACC GTGCCTTCCAGCTCTCTGGGAACCCAGACCTACATCTGCAATGTGAACCACA AGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCCTGCGGATC TTCTGGCGGCGGAGGATCTGGCGGAGGTGGTAGTTCAGGCGGAGTGTTCACC CTGGAAGATTTCGTCGGCGACTGGGAGCAGACCGCCGCCTATAATCTGGACC AGGTGCTGGAACAAGGCGGCGTTAGTTCCCTGCTGCAGAACCTGGCTGTGTC

		TGTGACCCCTATCCAGAGAATCGTGCGGAGCGGCGAGAACGCCCTGAAGATC GATATCCACGTGATCATCCCTTACGAGGGCCTGAGCGCCGATCAGATGGCTC AGATCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTTCAA AGTGATCCTGCCTTACGGCACCCTCGTGATCGATGGCGTGACCCCAAACATG CTGAACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCAAGA AAATCACCGTGACCGGCACACTGTGGAATGGCAACAAGATCATCGACGAGCG GCTGATCACCCCTGACGGCTCCATGCTGTTCAGAGTGACCATCAACAGCTGA TGA
SEQ ID NO: 14	α-CTLA4 light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGGCACATTGTCTCTGAGTCC TGGCGAGAGAGCTACCCTGTCTTGCAGAGCTTCCCAGTCCGTGGGATCTTCC TACCTGGCCTGGTATCAGCAGAAGCCTGGACAGGCTCCCAGACTGCTGATCT ACGGCGCCTTTTCTAGAGCCACAGGCATCCCTGACAGATTCTCCGGCTCTGG CTCTGGCACCGACTTCACCCTGACCATCTCTAGACTGGAACCCGAGGACTTC GCCGTGTACTACTGCCAGCAGTATGGCTCCTCTCCTTGGACCTTTGGACAGG GCACCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTT CCCACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTG CTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATG CCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGA CTCTACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCG TGACCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGGTGGCGGAGGATC TGGCGGAGGCGGATCTAGTGGCGGAGTGACCGGCTACAGACTGTTCGAAGAG ATCCTGTAATGA
SEQ ID NO: 15	α-CTLA4 light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGGCACACTGTCACTGTCTCC AGGCGAGAGAGCTACCCTGTCCTGTAGAGCCTCTCAGTCCGTGGGCTCCTCT TACCTGGCTTGGTATCAGCAGAAGCCCGGCCAGGCTCCTAGACTGTTGATCT ACGGCGCCTTCTCCAGAGCCACAGGCATCCCTGATAGATTCTCCGGCTCTGG CTCTGGCACCGACTTCACCCTGACCATCTCCAGACTGGAACCCGAGGACTTC GCCGTGTACTACTGTCAGCAGTACGGCTCCTCTCCTTGGACCTTTGGCCAGG GCACCAAGGTGGAAATCAAGCGGACAGTGGCCGCTCCTTCCGTGTTCATCTT CCCACCTTCCGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTG CTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATG CCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGA CAGCACCTACAGCCTGTCCTCCACACTGACCCTGTCCAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGCGAAGTGACCCATCAGGGCCTGTCTAGCCCTG TGACCAAGTCTTTCAACCGGGGCGAGTGCTGATGA
SEQ ID NO: 16	α-IFN heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAAGTGCAGTTGGTGCAGTCTGGCGCCGAAGTGAAGAAGCCTGG CGAGTCCCTGAAGATCTCCTGCAAAGGCTCCGGCTACATCTTCACCAACTAC TGGATCGCCTGGGTCCGACAGATGCCTGGCAAAGGCCTGGAATCCATGGGCA TCATCTACCCCGGCGACTCCGACATCAGATACAGCCCATCTTTCCAGGGCCA AGTGACCATCTCCGCCGACAAGTCTATCACCACCGCCTACCTGCAGTGGTCC TCTCTGAAGGCCTCTGACACCGCCATGTACTACTGCGCCAGACACGACATCG AGGGCTTCGATTATTGGGGCAGAGGCACCCTGGTCACCGTGTCCTCTGCTTC TACAAAGGGCCCCTCTGTGTTCCCTCTGGCTCCTTCCTCTAAATCCACCTCT GGCGGAACCGCTGCTCTGGGCTGTCTGGTCAAGGATTACTTCCCTGAGCCTG TGACCGTGTCTTGGAACTCTGGTGCTCTGACATCCGGCGTGCACACCTTTCC AGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTG CCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGC

		CTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCTTGCGGATCTTC TGGTGGCGGAGGATCTGGCGGAGGCGGATCTAGTGGCGGAGTGTTCACCCTG GAAGATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATAATCTGGACCAGG TTCTGGAACAAGGCGGCGTCAGCTCTCTGCTGCAGAATCTGGCTGTGTCTGT GACCCCTATCCAGAGAATCGTGCGCTCTGGCGAGAACGCTCTGAAGATCGAC ATCCACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATCAGATGGCTCAGA TCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTTCAAAGT GATCCTGCCTTACGGCACCCTCGTGATCGATGGCGTGACCCCAAACATGCTG AACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCAAGAAAA TCACCGTGACCGGCACACTGTGGAACGGCAACAAGATCATCGACGAGCGGCT GATCACCCCTGACGGCTCTATGCTGTTCCGCGTGACCATCAACTCCTAATGA
SEQ ID NO: 17	α-IFN light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGGCACATTGTCTCTGAGTCC TGGCGAGAGAGCTACCCTGTCTTGCAGAGCTTCCCAGTCCGTGTCCTCTAGC TTCTTCGCCTGGTATCAGCAGAAGCCCGGACAGGCTCCTAGACTGCTGATCT ACGGCGCCTCTTCTAGAGCCACAGGCATCCCTGATAGACTGTCCGGCTCTGG CTCTGGCACCGACTTTACCCTGACCATCACCAGACTGGAACCCGAGGACTTC GCCGTGTACTACTGCCAGCAGTACGACTCCTCTGCCATCACCTTTGGCCAGG GCACAAGACTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTT CCCACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTG CTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATG CCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGA CTCTACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCG TGACCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGGTGGCGGAGGATC TGGCGGAGGCGGATCTAGTGGCGGAGTGACCGGCTACAGACTGTTCGAAGAG ATCCTGTAATGA
SEQ ID NO: 18	α-IFN light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGGCACATTGTCTCTGAGTCC TGGCGAGAGAGCTACCCTGTCTTGCAGAGCTTCCCAGTCCGTGTCCTCTAGC TTCTTCGCCTGGTATCAGCAGAAGCCCGGACAGGCTCCTAGACTGCTGATCT ACGGCGCCTCTTCTAGAGCCACAGGCATCCCTGATAGACTGTCCGGCTCTGG CTCTGGCACCGACTTTACCCTGACCATCACCAGACTGGAACCCGAGGACTTC GCCGTGTACTACTGCCAGCAGTACGACTCCTCTGCCATCACCTTTGGCCAGG GCACAAGACTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTT CCCACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTG CTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATG CCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGA CTCTACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCG TGACCAAGTCTTTCAACAGAGGCGAGTGCTAATGA
SEQ ID NO: 19	α-IFNα heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGTTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCTGG CGCTTCTGTGAAGGTGTCCTGCAAGGCCTCTGGCTACACCTTTACCAGCTAC TCCATCTCCTGGGTCCGACAGGCTCCTGGACAAGGATTGGAGTGGATGGGCT GGATCTCCGTGTACAACGGCAACACCAACTACGCCCAGAAATTCCAGGGCAG AGTGACCATGACCACCGACACCTCTACCTCCACCGCCTACCTGGAACTGAGA TCCCTGAGATCTGACGACACCGCCGTGTACTACTGCGCCAGAGATCCTATCG CTGCTGGCTATTGGGGACAGGGCACACTGGTTACCGTGTCCTCTGCTTCTAC CAAGGGACCCTCTGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACCTCTGGT GGAACCGCTGCTCTGGGCTGTCTGGTCAAGGATTACTTCCCTGAGCCTGTGA

		CCGTGTCTTGGAACTCTGGTGCTCTGACCTCCGGCGTGCACACATTTCCAGC TGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCT TCTAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCTT CCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCTTGCGGATCTTCTGG TGGCGGAGGATCTGGCGGAGGTGGAAGTAGTGGCGGAGTGTTCACCCTGGAA GATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATAATCTGGACCAGGTTC TGGAACAAGGCGGCGTCAGCTCTCTGCTGCAGAATCTGGCTGTGTCTGTGAC CCCTATCCAGAGAATTGTGCGCTCTGGCGAGAACGCCCTGAAGATCGACATC CACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATCAGATGGCTCAGATCG AAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTTCAAAGTGAT CCTGCCTTACGGCACCCTGGTCATCGATGGCGTGACCCCAAACATGCTGAAC TACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCAAGAAAATCA CCGTGACCGGCACACTGTGGAACGGAAACAAGATCATCGACGAGCGGCTGAT CACCCCTGACGGCTCTATGCTGTTCCGCGTGACCATCAACTCCTAATGA
SEQ ID NO: 20	α-IFNα light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGGCACATTGTCTCTGAGTCC TGGCGAGAGAGCTACCCTGTCTTGCAGAGCTTCCCAGTCCGTGTCCTCTACC TACCTGGCCTGGTATCAGCAGAAGCCTGGACAGGCTCCCAGACTGCTGATCT ACGGCGCCTCTTCTAGAGCCACAGGCATCCCTGACAGATTCTCCGGCTCTGG CTCTGGCACCGACTTCACCCTGACCATCTCTAGACTGGAACCCGAGGACTTC GCCGTGTACTACTGCCAGCAGTATGGCTCCTCTCCTCGGACCTTTGGACAGG GCACCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTT CCCACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTG CTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATG CCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGA CTCTACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCG TGACCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGGTGGCGGAGGATC TGGCGGAGGCGGATCTAGTGGCGGAGTGACCGGCTACAGACTGTTCGAAGAG ATCCTGTAATGA
SEQ ID NO: 21	α-IFNα light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGGCACATTGTCTCTGAGTCC TGGCGAGAGAGCTACCCTGTCTTGCAGAGCTTCCCAGTCCGTGTCCTCTACC TACCTGGCCTGGTATCAGCAGAAGCCTGGACAGGCTCCCAGACTGCTGATCT ACGGCGCCTCTTCTAGAGCCACAGGCATCCCTGACAGATTCTCCGGCTCTGG CTCTGGCACCGACTTCACCCTGACCATCTCTAGACTGGAACCCGAGGACTTC GCCGTGTACTACTGCCAGCAGTATGGCTCCTCTCCTCGGACCTTTGGACAGG GCACCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTT CCCACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTG CTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATG CCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGA CTCTACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCG TGACCAAGTCTTTCAACAGAGGCGAGTGCTAATGA
SEQ ID NO: 22	α-IGF1R heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCCAGGTCCAGCTGCAAGAATCTGGCCCTGGACTGGTCAAGCCTTC TGGCACCCTGTCTCTGACATGTGCTGTGTCCGGCGGCTCCATCTCCTCCTCT AATTGGTGGTCTTGGGTCCGACAGCCTCCTGGCAAAGGACTGGAATGGATCG GCGAGATCTACCACTCCGGCTCCACCAACTACAACCCCAGCCTGAAGTCCAG AGTGACCATCTCCGTGGACAAGTCCAAGAACCAGTTCTCCCTGAAGCTGTCC TCTGTGACCGCTGCCGATACCGCCGTGTACTACTGTGCTAGATGGACCGGCA

		GAACCGACGCCTTTGATATCTGGGGCCAGGGCACAATGGTCACCGTGTCCTC TGCTTCTACCAAGGGACCCTCTGTGTTCCCTCTGGCTCCTTCCAGCAAGTCT ACCTCTGGTGGAACCGCTGCTCTGGGCTGCCTGGTCAAGGATTACTTTCCTG AGCCTGTGACCGTGTCTTGGAACTCTGGTGCTCTGACCTCCGGCGTGCACAC ATTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTACTCTCTGTCTAGCGTCGTG ACCGTGCCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACC ACAAGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCTTGCGG ATCTTCTGGTGGCGGAGGATCTGGCGGAGGTGGAAGTAGTGGCGGAGTGTTC ACCCTGGAAGATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATAATCTGG ACCAGGTTCTGGAACAAGGCGGCGTCAGCTCTCTGCTGCAGAATCTCGCTGT GTCTGTGACCCCTATCCAGAGAATCGTGCGCTCTGGCGAGAACGCCCTGAAG ATCGACATCCACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATCAGATGG CTCAGATCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTT CAAAGTGATCCTGCCTTACGGCACCCTGGTCATCGATGGCGTGACCCCAAAC ATGCTGAACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCA AGAAAATCACCGTGACCGGCACACTGTGGAACGGCAACAAGATCATCGACGA GCGGCTGATCACCCCTGACGGCTCTATGCTGTTCCGCGTGACCATCAACTCC TAATGA
SEQ ID NO: 23	α-IGF1R light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGACGTCGTGATGACCCAGTCTCCTCTGTCTCTGCCTGTGACACC TGGCGAGCCTGCCTCCATCTCTTGCAGATCTTCTCAGTCCCTGCTGCACTCC AACGGCTACAACTACCTGGACTGGTATCTGCAGAAGCCCGGCCAGTCTCCAC AGCTGCTGATCTACCTGGGCTCTAACAGAGCCTCTGGCGTGCCCGATAGATT CTCTGGCTCTGGATCTGGCACCGACTTCACCCTGAAGATCTCCAGAGTGGAA GCCGAGGACGTGGGCGTGTACTACTGTATGCAGGGCACCCACTGGCCTCTGA CCTTTGGACAGGGCACCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTC CGTGTTCATCTTCCCACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCT GTCGTGTGCCTGCTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGA AGGTGGACAATGCCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCA GGACTCCAAGGACTCTACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAG GCCGACTACGAGAAGCACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGAC TGTCTAGCCCCGTGACCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGG TGGCGGAGGATCTGGCGGAGGTGGAAGTAGTGGCGGCGTGACCGGCTACAGA CTGTTCGAAGAGATCCTGTAATGA
SEQ ID NO: 24	α-IGF1R light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGACGTCGTGATGACCCAGTCTCCTCTGTCTCTGCCTGTGACACC TGGCGAGCCTGCCTCCATCTCTTGCAGATCTTCTCAGTCCCTGCTGCACTCC AACGGCTACAACTACCTGGACTGGTATCTGCAGAAGCCCGGCCAGTCTCCAC AGCTGCTGATCTACCTGGGCTCTAACAGAGCCTCTGGCGTGCCCGATAGATT CTCTGGCTCTGGATCTGGCACCGACTTCACCCTGAAGATCTCCAGAGTGGAA GCCGAGGACGTGGGCGTGTACTACTGTATGCAGGGCACCCACTGGCCTCTGA CCTTTGGACAGGGCACCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTC CGTGTTCATCTTCCCACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCT GTCGTGTGCCTGCTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGA AGGTGGACAATGCCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCA GGACTCCAAGGACTCTACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAG GCCGACTACGAGAAGCACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGAC TGTCTAGCCCCGTGACCAAGTCTTTCAACAGAGGCGAGTGCTAATGA
SEQ ID NO:	α-IGF1R heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAAGTGCAGTTGTTGCAGTCTGGCGGAGGATTGGTTCAGCCTGG CGGATCTCTGAGACTGTCTTGTGCCGCCTCCGGCTTCATGTTCAGCAGATAC

25		CCTATGCACTGGGTCCGACAGGCCCCTGGAAAAGGACTGGAATGGGTCGGAT CTATCTCTGGCAGTGGCGGCGCTACCCCTTACGCTGATTCTGTGAAGGGCAG ATTCACCATCAGCCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGAGAGCCGAGGACACCGCCGTGTACTACTGCGCCAAGGACTTCTATC AGATCCTGACCGGCAACGCCTTCGATTATTGGGGCCAGGGCACAACCGTGAC CGTGTCCTCTGCTTCTACCAAGGGACCCTCTGTGTTCCCTCTGGCTCCTTCC AGCAAGTCTACCTCTGGTGGAACCGCTGCTCTGGGCTGCCTGGTCAAGGATT ACTTTCCTGAGCCTGTGACAGTGTCCTGGAACTCTGGTGCTCTGACCTCCGG CGTGCACACATTTCCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCC TCTGTCGTGACAGTGCCTTCCAGCTCTCTGGGCACCCAGACCTACATCTGCA ACGTGAACCACAAGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAA GTCTTGCGGATCTTCTGGTGGCGGTGGAAGTGGCGGAGGTGGAAGTTCAGGC GGAGTGTTCACCCTGGAAGATTTCGTCGGCGATTGGGAGCAGACCGCCGCCT ATAATCTGGACCAGGTTCTGGAACAAGGCGGCGTTAGCTCTCTGCTGCAGAA TCTGGCTGTGTCTGTGACCCCTATCCAGAGAATCGTGCGCTCTGGCGAGAAC GCCCTGAAGATCGACATCCACGTGATCATCCCTTACGAGGGCCTGTCTGCCG ATCAGATGGCTCAGATCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGA CCACCACTTCAAAGTGATCCTGCCTTACGGCACCCTGGTCATCGATGGCGTG ACCCCAAACATGCTGAACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGT TCGACGGCAAGAAAATCACCGTGACAGGCACCCTGTGGAACGGCAACAAGAT CATCGACGAGCGGCTGATCACCCCTGACGGCTCTATGCTGTTCAGAGTGACC ATCAACTCCTAATGA
SEQ ID NO: 26	α-IGF1R light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGCGACATCCAGATGACCCAGTCTCCAAGCTCTCTGTCTGCCTCTCT GGGCGACAGAGTGACCATCACCTGTAGAGCCTCTCAGGGCATCTCCTCCTAC CTGGCCTGGTATCAGCAGAAGCCTGGCAAGGCTCCCAAGCTGCTGATCTACG CTAAGTCTACCCTGCAGTCCGGCGTGCCCTCTAGATTTTCTGGCTCTGGATC TGGCACCGACTTCACCCTGACCATCAGTTCTCTGCAGCCTGAGGACTCCGCC ACCTACTACTGTCAGCAGTACTGGACCTTTCCTCTGACCTTCGGCGGAGGCA CCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC TGCAGAGCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACTC TACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCGTGA CCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGGCGGCGGAGGAAGCGG AGGCGGAGGATCTAGCGGCGGAGTTACCGGCTACAGACTGTTCGAAGAGATC CTGTAATGA
SEQ ID NO: 27	α-IGF1R light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACCGGCGACATCCAGATGACCCAGTCTCCATCCTCTCTGTCTGCCAGCCT GGGCGACAGAGTGACCATCACCTGTAGAGCCTCTCAGGGCATCTCCTCCTAC CTGGCCTGGTATCAGCAGAAGCCTGGCAAGGCTCCCAAGCTGCTGATCTACG CCAAGAGCACACTGCAGTCTGGCGTGCCCTCTAGATTCTCCGGCTCTGGCTC TGGCACCGACTTTACCCTGACAATCTCCAGCCTGCAGCCTGAGGACTCCGCC ACCTACTACTGTCAGCAGTACTGGACCTTTCCACTGACCTTCGGCGGAGGCA CCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCTTCCGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAAGTGCAGTGGAAGGTGGACAACGCTC TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACAG CACCTACAGCCTGTCCTCCACACTGACCCTGTCCAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGCGAAGTGACCCATCAGGGCCTGTCTAGCCCTGTGA

		CCAAGTCTTTCAACCGGGGCGAGTGCTGATGA
SEQ ID NO: 28	α-IGF1R heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAAGTGCAGTTGGTTCAGTCTGGCGGAGGACTGGTTAAGCCTGG CGGATCTCTGAGACTGTCTTGTGCCGCCTCTGGCTTCACCTTCTCTAGCTTT GCCATGCACTGGGTCCGACAGGCCCCTGGAAAAGGCCTGGAATGGATCTCCG TGATCGATACCAGAGGCGCCACCTACTACGCCGACTCTGTGAAGGGCAGATT CACCATCTCTCGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAACAGC CTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCCAGACTGGGCAACTTCT ACTACGGCATGGATGTGTGGGGCCAGGGCACAACAGTGACCGTGTCCTCTGC TTCTACCAAGGGACCCTCTGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACC TCTGGTGGAACCGCTGCTCTGGGCTGCCTGGTCAAGGATTACTTTCCTGAGC CTGTGACAGTGTCCTGGAACTCTGGTGCTCTGACCTCCGGCGTGCACACATT TCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCCTCTGTCGTGACC GTGCCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACA AGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCTTGCGGATC TTCTGGTGGCGGTGGAAGCGGAGGCGGAGGATCTAGTGGCGGAGTGTTCACC CTGGAAGATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATAATCTGGACC AGGTTCTGGAACAAGGCGGCGTCAGCTCTCTGCTGCAGAATCTGGCTGTGTC TGTGACCCCTATCCAGAGAATCGTGCGCTCTGGCGAGAACGCCCTGAAGATC GACATCCACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATCAGATGGCTC AGATCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTTCAA AGTGATCCTGCCTTACGGCACCCTGGTCATCGATGGCGTGACCCCAAACATG CTGAACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCAAGA AAATCACCGTGACCGGCACACTGTGGAACGGCAACAAGATCATCGACGAGCG GCTGATCACCCCTGACGGCTCCATGCTGTTTAGAGTGACCATCAACTCCTAA TGA
SEQ ID NO: 29	α-IGF1R light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGGCACATTGTCTGTGTCTCC CGGCGAGAGAGCTACCCTGTCTTGTAGAGCTTCCCAGTCCATCGGCTCCAGC CTGCACTGGTATCAGCAGAAACCTGGACAGGCCCCTCGGCTGCTGATTAAGT ACGCCTCTCAGTCCCTGTCTGGCATCCCTGACAGATTCTCTGGCTCTGGCTC CGGCACCGACTTCACCCTGACAATCTCTAGACTGGAACCCGAGGACTTCGCC GTGTACTACTGCCACCAGTCTAGCAGACTGCCTCACACCTTTGGCCAGGGCA CCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCATCTGACGAGCAGCTGAAGTCTGGCACCGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACTC TACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCGTGA CCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGGTGGCGGAGGATCTGG CGGAGGTGGAAGTAGTGGCGGCGTGACCGGCTACAGACTGTTCGAAGAGATC CTGTAATGA
SEQ ID NO: 30	α-IGF1R light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGGCACATTGTCTGTGTCTCC CGGCGAGAGAGCTACCCTGTCTTGTAGAGCTTCCCAGTCCATCGGCTCCAGC CTGCACTGGTATCAGCAGAAACCTGGACAGGCCCCTCGGCTGCTGATTAAGT ACGCCTCTCAGTCCCTGTCTGGCATCCCTGACAGATTCTCTGGCTCTGGCTC CGGCACCGACTTCACCCTGACAATCTCTAGACTGGAACCCGAGGACTTCGCC GTGTACTACTGCCACCAGTCTAGCAGACTGCCTCACACCTTTGGCCAGGGCA CCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCATCTGACGAGCAGCTGAAGTCTGGCACCGCTTCTGTCGTGTGCCTGCTG

		AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACTC TACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCGTGA CCAAGTCTTTCAACAGAGGCGAGTGCTAATGA
SEQ ID NO: 31	α-IGF1R heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACCGGACAGGTGGAACTGGTTGAATCTGGTGGCGGAGTGGTGCAGCCTGG CAGATCTCAGAGACTGTCTTGTGCCGCCTCTGGCTTCACCTTCTCCTCTTAC GGCATGCACTGGGTCCGACAGGCCCCTGGAAAAGGACTGGAATGGGTCGCCA TCATTTGGTTCGACGGCTCCTCTACCTACTACGCCGATTCTGTGCGGGGCAG ATTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGAGAGCCGAGGATACCGCCGTGTACTTCTGTGCCAGAGAGCTGGGGA GAAGATACTTCGATCTGTGGGGCAGAGGCACCCTGGTGTCTGTGTCCTCTGC TTCTACCAAGGGACCCAGCGTTTTCCCTCTGGCTCCATCCTCTAAGTCCACC TCTGGTGGAACCGCTGCTCTGGGCTGTCTGGTCAAGGATTACTTCCCTGAGC CTGTGACCGTGTCCTGGAACTCTGGTGCTCTGACATCCGGCGTGCACACCTT TCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCCTCTGTCGTGACC GTGCCTTCTTCTAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACA AGCCTTCCAACACCAAAGTGGACAAGAGAGTGGAACCCAAGTCTTGCGGATC TTCTGGCGGCGGAGGAAGCGGAGGCGGAGGATCTAGCGGCGGAGTGTTCACC CTGGAAGATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATAATCTGGACC AGGTTCTGGAACAAGGCGGCGTGTCCTCTCTGCTGCAGAATCTGGCTGTGTC TGTGACCCCTATCCAGAGAATCGTGCGCTCTGGCGAGAACGCCCTGAAGATC GACATCCACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATCAGATGGCCC AGATTGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTTCAA AGTGATCCTGCCTTACGGCACCCTCGTGATCGATGGCGTGACCCCAAACATG CTGAACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGATGGCAAGA AAATCACCGTGACCGGCACACTGTGGAACGGCAACAAGATCATCGACGAGCG GCTGATCACCCCTGACGGCTCTATGCTGTTCAGAGTGACCATCAACTCCTAA TGA
SEQ ID NO: 32	α-IGF1R light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGCCACATTGTCTCTGAGTCC TGGCGAGAGAGCTACCCTGTCTTGCAGAGCTTCCCAGTCCGTGTCCTCCTAC CTGGCCTGGTATCAGCAGAAACCTGGACAGGCCCCTCGGCTGCTGATCTACG ATGCTTCTAAGAGAGCCACAGGCATCCCCGCCAGATTTTCTGGCTCTGGATC TGGCACCGACTTCACCCTGACCATCTCTAGCCTGGAACCTGAGGACTTCGCC GTGTACTACTGCCAGCAGAGATCCAAGTGGCCTCCTTGGACCTTTGGACAGG GCACCAAGGTGGAATCTAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTT CCCACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTG CTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATG CCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGA CTCTACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCG TGACCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGGTGGCGGAGGATC TGGCGGAGGCGGATCTAGTGGCGGAGTGACCGGCTACAGACTGTTCGAAGAG ATCCTGTAATGA
SEQ ID NO: 33	α-IGF1R light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGCCACATTGTCTCTGAGTCC TGGCGAGAGAGCTACCCTGTCTTGCAGAGCTTCCCAGTCCGTGTCCTCCTAC CTGGCCTGGTATCAGCAGAAACCTGGACAGGCCCCTCGGCTGCTGATCTACG ATGCTTCTAAGAGAGCCACAGGCATCCCCGCCAGATTTTCTGGCTCTGGATC

		TGGCACCGACTTCACCCTGACCATCTCTAGCCTGGAACCTGAGGACTTCGCC GTGTACTACTGCCAGCAGAGATCCAAGTGGCCTCCTTGGACCTTTGGACAGG GCACCAAGGTGGAATCTAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTT CCCACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTG CTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATG CCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGA CTCTACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCG TGACCAAGTCTTTCAACAGAGGCGAGTGCTAATGA
SEQ ID NO: 34	α-IL6R heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGGTGCAGTTGGTTGAATCTGGCGGAGGACTGGTGCAGCCTGG CAGATCTCTGAGACTGTCTTGCGCCGCCTCCAGATTCACCTTCGACGATTAC GCCATGCACTGGGTCCGACAGGCCCCTGGAAAAGGATTGGAGTGGGTGTCCG GCATCTCCTGGAACTCTGGCAGAATCGGCTACGCCGACTCCGTGAAGGGCAG ATTCACAATCTCCCGGGACAACGCCGAGAACTCCCTGTTCCTGCAGATGAAT GGCCTGAGAGCCGAGGACACCGCTCTGTACTATTGCGCCAAGGGCAGAGACT CCTTCGATATCTGGGGCCAGGGCACCATGGTCACCGTGTCCTCTGCTTCTAC CAAGGGACCCTCTGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACCTCTGGT GGAACCGCTGCTCTGGGCTGCCTGGTCAAGGATTACTTTCCTGAGCCTGTGA CCGTGTCTTGGAACTCCGGTGCTCTGACATCCGGCGTGCACACATTTCCAGC TGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCT TCTAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCTT CCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCTTGCGGATCTTCTGG TGGCGGTGGAAGCGGAGGCGGAGGATCTAGTGGCGGAGTGTTCACCCTGGAA GATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATAATCTGGACCAGGTTC TGGAACAAGGCGGCGTCAGCTCTCTGCTGCAGAATCTGGCTGTGTCTGTGAC CCCTATCCAGAGAATCGTGCGCTCTGGCGAGAACGCCCTGAAGATCGACATC CACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATCAGATGGCTCAGATCG AAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTTCAAAGTGAT CCTGCCTTACGGCACCCTGGTCATCGATGGCGTGACCCCAAACATGCTGAAC TACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCAAGAAAATCA CCGTGACCGGCACACTGTGGAACGGCAACAAGATCATCGACGAGCGGCTGAT CACCCCTGACGGCTCTATGCTGTTCAGAGTGACCATCAACTCCTAATGA
SEQ ID NO: 35	α-IL6R light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGCGACATCCAGATGACCCAGTCTCCATCCTCTGTGTCTGCCTCTGT GGGCGACAGAGTGACCATCACCTGTAGAGCCTCTCAGGGCATCTCTAGCTGG CTGGCCTGGTATCAGCAGAAGCCTGGAAAGGCCCCTAAGCTGCTGATCTACG GCGCCTCTTCTCTGGAATCTGGCGTGCCCTCTAGATTCTCCGGCTCTGGCTC TGGCACCGACTTTACCCTGACAATCAGCTCCCTGCAGCCTGAGGACTTCGCC TCTTACTACTGCCAGCAGGCCAACAGCTTCCCCTATACCTTTGGCCAGGGCA CCAAGCTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACTC TACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCGTGA CCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGGTGGCGGAGGATCTGG CGGAGGTGGAAGTAGTGGCGGCGTGACCGGCTACAGACTGTTCGAAGAGATC CTGTAATGA
SEQ ID	α-IL6R light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGCGACATCCAGATGACCCAGTCTCCATCCTCTGTGTCTGCCTCTGT

NO: 36		GGGCGACAGAGTGACCATCACCTGTAGAGCCTCTCAGGGCATCTCTAGCTGG CTGGCCTGGTATCAGCAGAAGCCTGGAAAGGCCCCTAAGCTGCTGATCTACG GCGCCTCTTCTCTGGAATCTGGCGTGCCCTCTAGATTCTCCGGCTCTGGCTC TGGCACCGACTTTACCCTGACAATCAGCTCCCTGCAGCCTGAGGACTTCGCC TCTTACTACTGCCAGCAGGCCAACAGCTTCCCCTATACCTTTGGCCAGGGCA CCAAGCTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACTC TACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCGTGA CCAAGTCTTTCAACAGAGGCGAGTGCTAATGA
SEQ ID NO: 37	α-LINGO-1 heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGGTGCAGTTGTTGGAATCTGGCGGAGGATTGGTGCAGCCTGG CGGATCTCTGAGACTGTCTTGTGCCGCCTCTGGCTTCACCTTCTCCGCCTAT GAGATGAAGTGGGTCCGACAGGCTCCTGGCAAAGGACTGGAATGGGTGTCCG TGATTGGCCCTTCTGGCGGCTTTACCTTTTACGCCGACTCCGTGAAGGGCAG ATTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCCACCGAGGGCGACA ACGACGCCTTTGATATTTGGGGCCAGGGCACCACCGTGACCGTGTCCTCTGC TTCTACAAAGGGCCCCTCTGTGTTCCCTCTGGCTCCTTCCTCTAAATCCACC TCTGGCGGAACCGCTGCTCTGGGCTGTCTGGTCAAGGATTACTTCCCTGAGC CTGTGACAGTGTCCTGGAACTCTGGTGCTCTGACATCCGGCGTGCACACCTT TCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCCTCTGTCGTGACA GTGCCTTCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACA AGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCTTGCGGATC TTCCGGCGGAGGTGGAAGTGGCGGAGGCGGATCAAGCGGCGGAGTGTTCACA CTGGAAGATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATAATCTGGACC AGGTTCTGGAACAAGGCGGCGTTAGCTCTCTGCTGCAGAATCTGGCTGTGTC TGTGACCCCTATCCAGAGAATCGTGCGCTCTGGCGAGAACGCCCTGAAGATC GACATCCACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATCAGATGGCTC AGATCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTTCAA AGTGATCCTGCCTTACGGCACCCTGGTCATCGATGGCGTGACCCCAAACATG CTGAACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCAAGA AAATCACCGTGACAGGCACCCTGTGGAACGGCAACAAGATCATCGACGAGCG GCTGATCACCCCTGACGGCTCTATGCTGTTCAGAGTGACCATCAACTCCTAA TGA
SEQ ID NO: 38	α-LINGO-1 light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGATATCCAGATGACCCAGTCTCCTGCCACATTGTCTCTGAGTCC TGGCGAGAGAGCTACCCTGTCTTGCAGAGCTTCCCAGTCCGTGTCCTCCTAC CTGGCCTGGTATCAGCAGAAACCTGGACAGGCCCCTCGGCTGCTGATCTACG ATGCCTCTAATAGAGCCACAGGCATCCCCGCCAGATTCTCTGGCTCTGGATC TGGCACCGACTTCACCCTGACCATCTCTAGCCTGGAACCTGAGGACTTCGCC GTGTACTACTGCCAGCAGAGATCCAACTGGCCTATGTACACCTTCGGCCAGG GCACCAAGCTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTT CCCACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTG CTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATG CCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGA CTCTACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCG TGACCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGGTGGCGGAGGAAG

		CGGAGGCGGAGGATCATCTGGCGGAGTGACCGGCTACAGACTGTTCGAAGAG ATCCTGTAATGA
SEQ ID NO: 39	α-LINGO-1 light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGATATCCAGATGACCCAGTCTCCTGCCACATTGTCTCTGAGTCC TGGCGAGAGAGCTACCCTGTCTTGCAGAGCTTCCCAGTCCGTGTCCTCCTAC CTGGCCTGGTATCAGCAGAAACCTGGACAGGCCCCTCGGCTGCTGATCTACG ATGCCTCTAATAGAGCCACAGGCATCCCCGCCAGATTCTCTGGCTCTGGATC TGGCACCGACTTCACCCTGACCATCTCTAGCCTGGAACCTGAGGACTTCGCC GTGTACTACTGCCAGCAGAGATCCAACTGGCCTATGTACACCTTCGGCCAGG GCACCAAGCTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTT CCCACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTG CTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATG CCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGA CTCTACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCG TGACCAAGTCTTTCAACAGAGGCGAGTGCTAATGA
SEQ ID NO: 40	α-neuropilin 1 heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGGTGCAGTTGGTTGAATCTGGCGGAGGATTGGTGCAGCCTGG CGGATCTCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCTCTTAC GCTATGTCCTGGGTCCGACAGGCTCCTGGCAAAGGATTGGAGTGGGTGTCCC AGATTTCTCCCGCTGGCGGCTACACCAACTACGCCGATTCTGTGAAGGGCAG ATTCACCATCTCCGCCGACACCTCCAAGAACACCGCCTACCTGCAGATGAAC TCCCTGAGAGCTGAGGACACCGCCGTGTACTATTGTGCTAGAGGCGAGCTGC CCTACTACCGGATGTCCAAAGTGATGGATGTGTGGGGCCAGGGCACACTGGT TACCGTGTCCTCTGCTTCTACCAAGGGACCCTCTGTGTTCCCTCTGGCTCCT TCCAGCAAGTCTACCTCTGGTGGAACCGCTGCTCTGGGCTGCCTGGTCAAGG ATTACTTTCCTGAGCCTGTGACCGTGTCTTGGAACTCTGGTGCTCTGACCTC CGGCGTGCACACATTTCCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTG TCCTCTGTCGTGACCGTGCCTTCTAGCTCTCTGGGCACCCAGACCTACATCT GCAACGTGAACCACAAGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACC CAAGTCTTGCGGATCTTCTGGTGGCGGTGGAAGTGGCGGAGGTGGAAGTTCA GGCGGAGTGTTCACCCTGGAAGATTTCGTCGGCGATTGGGAGCAGACCGCCG CCTATAATCTGGACCAGGTTCTGGAACAAGGCGGCGTCAGCTCTCTGCTGCA GAATCTGGCTGTGTCTGTGACCCCTATCCAGAGAATCGTGCGCTCTGGCGAG AACGCCCTGAAGATCGACATCCACGTGATCATCCCTTACGAGGGCCTGTCTG CCGATCAGATGGCTCAGATCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGA CGACCACCACTTCAAAGTGATCCTGCCTTACGGCACCCTGGTCATCGATGGC GTGACCCCAAACATGCTGAACTACTTCGGCAGACCCTACGAGGGAATCGCCG TGTTCGACGGCAAGAAAATCACCGTGACCGGCACACTGTGGAACGGCAACAA GATCATCGACGAGCGGCTGATCACCCCTGACGGCTCTATGCTGTTCAGAGTG ACCATCAACTCCTAATGA
SEQ ID NO: 41	α-neuropilin 1 light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGCGACATCCAGATGACCCAGTCTCCATCCTCTCTGTCTGCCTCTGT GGGCGACAGAGTGACCATCACCTGTCGGGCCTCTCAGTACTTCTCCTCCTAC CTGGCCTGGTATCAGCAGAAGCCTGGCAAGGCTCCCAAGCTGCTGATCTACG GCGCCTCTTCTAGAGCCTCTGGCGTGCCATCTAGATTCTCCGGCTCTGGCTC TGGCACCGACTTTACCCTGACAATCAGCTCCCTGCAGCCTGAGGACTTCGCC ACCTACTACTGTCAGCAGTACCTGGGCTCTCCTCCAACCTTTGGCCAGGGCA CCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC

		TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACTC TACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCGTGA CCAAGTCTTTCAACAGAGGCGAGTGCGGATCTTCTGGTGGCGGAGGATCTGG CGGAGGTGGAAGTAGTGGCGGCGTGACCGGCTACAGACTGTTCGAAGAGATC CTGTAATGA
SEQ ID NO: 42	α-neuropilin 1 light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGCGACATCCAGATGACCCAGTCTCCATCCTCTCTGTCTGCCTCTGT GGGCGACAGAGTGACCATCACCTGTCGGGCCTCTCAGTACTTCTCCTCCTAC CTGGCCTGGTATCAGCAGAAGCCTGGCAAGGCTCCCAAGCTGCTGATCTACG GCGCCTCTTCTAGAGCCTCTGGCGTGCCATCTAGATTCTCCGGCTCTGGCTC TGGCACCGACTTTACCCTGACAATCAGCTCCCTGCAGCCTGAGGACTTCGCC ACCTACTACTGTCAGCAGTACCTGGGCTCTCCTCCAACCTTTGGCCAGGGCA CCAAGGTGGAAATCAAGAGAACCGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCATCTGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACTC TACCTACAGCCTGTCCTCCACACTGACCCTGTCTAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGTGAAGTGACCCACCAGGGACTGTCTAGCCCCGTGA CCAAGTCTTTCAACAGAGGCGAGTGCTAATGA
SEQ ID NO: 43	α-CD221 heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAAGTGCAGTTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCTGG CTCCTCTGTGAAGGTGTCCTGCAAGGCTTCTGGCGGCACCTTCTCCTCTTAC GCCATCTCTTGGGTCCGACAGGCTCCTGGACAAGGCTTGGAGTGGATGGGCG GCATCATCCCTATCTTCGGCACCGCCAACTACGCCCAGAAATTCCAGGGCAG AGTGACCATCACCGCCGACAAGTCTACCTCCACCGCCTACATGGAACTGTCC AGCCTGAGATCTGAGGACACCGCCGTGTACTACTGTGCTAGAGCCCCTCTGC GGTTCCTGGAATGGTCTACCCAGGACCACTACTACTATTACTACATGGACGT GTGGGGCAAGGGCACCACCGTGACAGTTTCTTCCGCTTCCACCAAGGGACCC AGCGTTTTCCCTCTGGCTCCATCCTCCAAGTCCACCTCTGGTGGAACAGCTG CTCTGGGCTGCCTGGTCAAGGATTACTTTCCTGAGCCTGTGACCGTGTCCTG GAACTCTGGTGCTCTGACATCCGGCGTGCACACCTTTCCAGCTGTGCTGCAG TCCTCTGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCTTCTAGCTCTC TGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCTTCCAACACCAA AGTGGACAAGAGAGTGGAACCCAAGTCTTGCGGATCTTCCGGTGGCGGAGGA TCTGGCGGAGGTGGAAGTAGTGGCGGAGTGTTCACCCTGGAAGATTTCGTCG GCGATTGGGAGCAGACCGCCGCCTATAATCTGGACCAGGTTCTGGAACAAGG CGGCGTGTCCTCTCTGCTGCAGAATCTGGCTGTGTCTGTGACCCCTATCCAG AGAATCGTGCGCTCTGGCGAGAACGCCCTGAAGATCGACATCCACGTGATCA TCCCTTACGAGGGCCTGTCTGCCGATCAGATGGCTCAGATCGAAGAGGTGTT CAAGGTGGTGTACCCCGTGGACGACCACCACTTCAAAGTGATCCTGCCTTAC GGCACCCTGGTCATCGATGGCGTGACCCCAAACATGCTGAACTACTTCGGCA GACCCTACGAGGGAATCGCCGTGTTCGACGGCAAGAAAATCACCGTGACCGG CACACTGTGGAACGGCAACAAGATCATCGACGAGCGGCTGATCACCCCTGAC GGCTCTATGCTGTTTAGAGTGACAATCAACTCCTAATGA
SEQ ID NO: 44	α-CD221 light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGATCCTCTGAGTTGACACAGGACCCTGCTGTGTCTGTGGCTCTGGG ACAGACAGTGCGGATTACCTGTCAGGGCGACTCCCTGAGATCTTACTACGCC ACCTGGTATCAGCAGAAGCCCGGACAGGCTCCCATCCTGGTTATCTACGGCG AGAACAAGCGGCCCTCTGGCATCCCTGATAGATTCTCTGGCTCCTCCTCCGG CAATACCGCCTCTCTGACAATTACTGGCGCCCAGGCTGAGGACGAGGCCGAC

		TACTATTGCAAGTCCAGAGATGGCTCTGGCCAGCACTTGGTGTTTGGCGGCG GAACAAAACTGACCGTGCTGGGCCAGCCTAAGGCCAATCCTACAGTGACCCT GTTTCCTCCATCCTCCGAGGAACTGCAGGCCAACAAGGCTACCCTCGTGTGC CTGATCTCTGACTTTTACCCTGGCGCTGTGACCGTGGCTTGGAAGGCTGATG GATCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCTAGCAAGCAGTCCAA CAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAGTGGAAG TCCCACCGGTCCTACTCTTGCCAAGTGACCCATGAGGGCTCCACCGTGGAAA AGACAGTGGCCCCTACCGAGTGCTCTGGATCTTCTGGTGGCGGAGGATCTGG CGGAGGTGGAAGTAGTGGCGGCGTGACCGGCTACAGACTGTTCGAAGAGATC CTGTAATGA
SEQ ID NO: 45	α-CD221 light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGCT CTACCGGATCCTCTGAGCTGACACAGGACCCTGCTGTGTCTGTGGCTCTGGG CCAGACAGTGCGGATTACCTGTCAGGGCGACTCCCTGAGATCCTACTACGCC ACCTGGTATCAGCAGAAGCCTGGACAGGCTCCCATCCTGGTCATCTACGGCG AGAACAAGCGGCCCTCTGGCATCCCTGATAGATTCTCCGGCTCCTCCAGCGG CAATACCGCCTCTCTGACAATTACCGGCGCTCAGGCTGAGGACGAGGCCGAC TACTACTGCAAGTCCAGAGATGGCTCCGGCCAGCACCTGGTTTTTGGCGGAG GAACAAAGCTGACCGTGCTGGGCCAGCCTAAGGCCAATCCTACCGTGACACT GTTCCCTCCATCCTCCGAGGAACTGCAGGCCAACAAGGCTACCCTCGTGTGC CTGATCTCCGACTTTTACCCTGGCGCTGTGACCGTGGCCTGGAAGGCTGATG GATCTCCTGTGAAGGCTGGCGTGGAAACCACCAAGCCTTCCAAGCAGTCCAA CAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAGTGGAAG TCCCACCGGTCCTACAGCTGCCAAGTGACCCATGAGGGCTCCACCGTGGAAA AGACCGTGGCTCCTACCGAGTGCTCCTGATGA
SEQ ID NO: 46	α-death receptor 5 heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAAGTGCAGTTGGTTCAGTCTGGCGGCGGAGTTGAAAGACCTGG CGGATCTCTGAGACTGTCTTGTGCCGCCTCTGGCTTCACCTTCGACGACTAC GCTATGTCCTGGGTCCGACAGGCTCCTGGCAAAGGATTGGAATGGGTGTCCG GCATCAACTGGCAAGGCGGCTCTACCGGCTACGCCGATTCTGTGAAGGGCAG AGTGACCATCTCTCGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAAC AGCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTGCTAAGATCCTCGGCG CTGGCAGAGGCTGGTACTTCGATTATTGGGGCAAGGGCACCACCGTGACCGT GTCCTCTGCTTCTACAAAGGGCCCCTCTGTGTTCCCTCTGGCTCCTTCCTCT AAATCCACCTCTGGCGGAACCGCTGCTCTGGGCTGTCTGGTCAAGGATTACT TCCCTGAGCCTGTGACAGTGTCCTGGAACTCTGGTGCTCTGACATCCGGCGT GCACACCTTTCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCCTCT GTCGTGACAGTGCCTTCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACG TGAACCACAAGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTC TTGTGGATCTTCTGGCGGAGGTGGAAGCGGAGGCGGAGGATCAAGTGGCGGA GTGTTCACCCTGGAAGATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATA ATCTGGACCAGGTTCTGGAACAAGGCGGCGTTAGCTCTCTGCTGCAGAATCT GGCTGTGTCTGTGACCCCTATCCAGAGAATCGTGCGCTCTGGCGAGAACGCC CTGAAGATCGACATCCACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATC AGATGGCTCAGATCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCA CCACTTCAAAGTGATCCTGCCTTACGGCACCCTGGTCATCGATGGCGTGACC CCAAACATGCTGAACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCG ACGGCAAGAAAATCACCGTGACAGGCACCCTGTGGAACGGCAACAAGATCAT CGACGAGCGGCTGATCACCCCTGACGGCTCCATGCTGTTTCGCGTGACCATC AACTCCTAATGA
SEQ ID	α-death receptor 5	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGATCCTCTGAGTTGACACAGGACCCTGCTGTGTCTGTGGCTCTGGG

NO: 47	light - SmBiT	ACAGACAGTGCGGATCACCTGTTCCGGCGACTCCCTGAGATCTTACTACGCC TCCTGGTATCAGCAGAAGCCTGGACAGGCTCCCGTGCTGGTTATCTACGGCG CCAACAACAGACCTTCTGGCATCCCTGACAGATTCTCCGGCTCCAGCTCTGG CAATACCGCCTCTCTGACAATTACCGGCGCTCAGGCTGAGGACGAGGCCGAC TACTACTGCAACTCTGCCGACTCTTCCGGCAATCACGTTGTGTTTGGCGGAG GCACCAAGCTGACAGTGCTGGGCCAACCTAAGGCCAATCCTACCGTGACACT GTTCCCTCCATCCTCCGAGGAACTGCAGGCTAACAAGGCTACCCTCGTGTGC CTGATCTCCGATTTTTACCCTGGCGCTGTGACCGTGGCTTGGAAGGCTGATG GATCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCTAGCAAGCAGTCCAA CAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAGTGGAAG TCCCACCGGTCCTACTCTTGCCAAGTGACCCATGAGGGCTCCACCGTGGAAA AGACAGTGGCCCCTACCGAGTGCTCTGGATCTTCTGGTGGCGGAGGAAGCGG AGGCGGAGGATCATCTGGCGGAGTGACCGGCTACAGACTGTTCGAAGAGATC CTGTAATGA
SEQ ID NO: 48	α-death receptor 5 light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGATCCTCTGAGTTGACACAGGACCCTGCTGTGTCTGTGGCTCTGGG ACAGACAGTGCGGATCACCTGTTCCGGCGACTCCCTGAGATCTTACTACGCC TCCTGGTATCAGCAGAAGCCTGGACAGGCTCCCGTGCTGGTTATCTACGGCG CCAACAACAGACCTTCTGGCATCCCTGACAGATTCTCCGGCTCCAGCTCTGG CAATACCGCCTCTCTGACAATTACCGGCGCTCAGGCTGAGGACGAGGCCGAC TACTACTGCAACTCTGCCGACTCTTCCGGCAATCACGTTGTGTTTGGCGGAG GCACCAAGCTGACAGTGCTGGGCCAACCTAAGGCCAATCCTACCGTGACACT GTTCCCTCCATCCTCCGAGGAACTGCAGGCTAACAAGGCTACCCTCGTGTGC CTGATCTCCGATTTTTACCCTGGCGCTGTGACCGTGGCTTGGAAGGCTGATG GATCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCTAGCAAGCAGTCCAA CAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAGTGGAAG TCCCACCGGTCCTACTCTTGCCAAGTGACCCATGAGGGCTCCACCGTGGAAA AGACAGTGGCCCCTACCGAGTGCTCTTAATGA
SEQ ID NO: 49	α-IL23 heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAAGTGCAGTTGGTGCAGTCTGGCGCCGAAGTGAAGAAGCCTGG CGAGTCCCTGAAGATCTCCTGCAAAGGCTCCGGCTACTCCTTCTCCAACTAC TGGATCGGCTGGGTCCGACAGATGCCTGGCAAAGGACTGGAATGGATGGGCA TCATCGACCCCTCCAACAGCTACACCAGATACAGCCCTAGCTTCCAGGGCCA AGTGACCATCTCCGCCGACAAGTCTATCTCCACCGCCTACCTGCAGTGGTCC TCTCTGAAGGCCTCTGACACCGCCATGTACTACTGCGCCAGATGGTACTACA AGCCCTTCGATGTGTGGGGCCAGGGCACACTGGTTACCGTGTCCTCTGCTTC TACCAAGGGACCCTCTGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACCTCT GGTGGAACCGCTGCTCTGGGCTGCCTGGTCAAGGATTACTTTCCTGAGCCTG TGACCGTGTCTTGGAACTCTGGTGCTCTGACCTCCGGCGTGCACACATTTCC AGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTG CCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGC CTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCTTGCGGATCTTC TGGTGGCGGAGGATCTGGCGGAGGTGGAAGTAGTGGCGGAGTGTTCACCCTG GAAGATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATAATCTGGACCAGG TTCTGGAACAAGGCGGCGTCAGCTCTCTGCTGCAGAATCTGGCTGTGTCTGT GACCCCTATCCAGAGAATCGTGCGCTCTGGCGAGAACGCTCTGAAGATCGAC ATCCACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATCAGATGGCTCAGA TCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTTCAAAGT GATCCTGCCTTACGGCACCCTGGTCATCGATGGCGTGACCCCAAACATGCTG AACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCAAGAAAA TCACCGTGACCGGCACACTGTGGAACGGCAACAAGATCATCGACGAGCGGCT

		GATCACCCCTGACGGCTCTATGCTGTTCCGCGTGACCATCAACTCCTAATGA
SEQ ID NO: 50	α-IL23 light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACAGGCCAGTCTGTTCTGACTCAGCCTCCTTCTGTTTCTGGCGCTCCTGG CCAGAGAGTGACCATCTCCTGTACCGGCTCCTCCTCTAACATCGGCTCTGGC TACGACGTGCACTGGTATCAGCAGCTGCCTGGCACAGCCCCTAAACTGCTGA TCTACGGCAACTCCAAGAGGCCTTCTGGCGTGCCCGATAGATTCTCCGGCTC TAAGTCTGGCACCTCTGCTTCTCTGGCTATCACCGGCCTGCAGTCTGAGGAC GAGGCCGATTACTACTGCGCTTCTTGGACCGATGGCCTGAGCCTGGTTGTGT TTGGCGGCGGAACAAAGCTGACAGTGCTGGGCCAGCCTAAGGCCAATCCTAC CGTGACACTGTTCCCTCCATCCTCCGAGGAACTGCAGGCTAACAAGGCTACC CTCGTGTGCCTGATCTCCGATTTTTACCCTGGCGCTGTGACCGTGGCTTGGA AGGCTGATGGATCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCTAGCAA GCAGTCCAACAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAA CAGTGGAAGTCCCACCGGTCCTACTCTTGCCAAGTGACCCATGAGGGCTCCA CCGTGGAAAAGACAGTGGCCCCTACCGAGTGCTCTGGATCTTCTGGTGGCGG AGGATCTGGCGGAGGTGGAAGTAGTGGCGGCGTGACCGGCTACAGACTGTTC GAAGAGATCCTGTAATGA
SEQ ID NO: 51	α-IL23 light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACAGGCCAGTCTGTTCTGACTCAGCCTCCTTCTGTTTCTGGCGCTCCTGG CCAGAGAGTGACCATCTCCTGTACCGGCTCCTCCTCTAACATCGGCTCTGGC TACGACGTGCACTGGTATCAGCAGCTGCCTGGCACAGCCCCTAAACTGCTGA TCTACGGCAACTCCAAGAGGCCTTCTGGCGTGCCCGATAGATTCTCCGGCTC TAAGTCTGGCACCTCTGCTTCTCTGGCTATCACCGGCCTGCAGTCTGAGGAC GAGGCCGATTACTACTGCGCTTCTTGGACCGATGGCCTGAGCCTGGTTGTGT TTGGCGGCGGAACAAAGCTGACAGTGCTGGGCCAGCCTAAGGCCAATCCTAC CGTGACACTGTTCCCTCCATCCTCCGAGGAACTGCAGGCTAACAAGGCTACC CTCGTGTGCCTGATCTCCGATTTTTACCCTGGCGCTGTGACCGTGGCTTGGA AGGCTGATGGATCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCTAGCAA GCAGTCCAACAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAA CAGTGGAAGTCCCACCGGTCCTACTCTTGCCAAGTGACCCATGAGGGCTCCA CCGTGGAAAAGACAGTGGCCCCTACCGAGTGCTCTTAATGA
SEQ ID NO: 52	α-HER3 heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGTTGGTTCAGTCTGGCGGAGGACTTGTTCAGCCAGG CGGATCTCTGAGACTGTCTTGTGCCGCCTCTGGCTTCACCTTCGACGATTAC GCTATGCACTGGGTCCGACAGGCCCCTGGAAAAGGATTGGAATGGGTGGCCG GCATCTCCTGGGATTCTGGCTCTACCGGCTACGCCGATTCCGTGAAGGGCAG ATTCACCATCTCTCGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAAC AGCCTGAGAGCCGAGGACACCGCTCTGTACTACTGTGCTAGAGATCTGGGCG CCTACCAGTGGGTGGAAGGCTTTGATTATTGGGGCCAGGGCACCCTGGTCAC CGTGTCCTCTGCTTCTACAAAGGGCCCCTCTGTGTTCCCTCTGGCTCCTTCC TCTAAATCCACCTCTGGCGGAACCGCTGCTCTGGGCTGTCTGGTCAAGGATT ACTTCCCTGAGCCTGTGACCGTGTCTTGGAACTCTGGTGCTCTGACATCCGG CGTGCACACCTTTCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCC TCTGTCGTGACCGTGCCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCA ACGTGAACCACAAGCCTAGCAACACCAAGGTGGACAAGAGAGTGGAACCCAA GTCTTGCGGATCTTCTGGCGGCGGAGGAAGCGGAGGCGGAGGATCTAGTGGC GGAGTGTTCACCCTGGAAGATTTCGTCGGCGATTGGGAGCAGACCGCCGCCT ATAATCTGGACCAGGTTCTGGAACAAGGCGGCGTCAGCTCTCTGCTGCAGAA TCTGGCTGTGTCTGTGACCCCTATCCAGAGAATCGTGCGCTCTGGCGAGAAC GCCCTGAAGATCGACATCCACGTGATCATCCCTTACGAGGGCCTGTCTGCCG ATCAGATGGCTCAGATCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGA

		CCACCACTTCAAAGTGATCCTGCCTTACGGCACCCTCGTGATCGATGGCGTG ACCCCAAACATGCTGAACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGT TCGACGGCAAGAAAATCACCGTGACCGGCACACTGTGGAACGGCAACAAGAT CATCGACGAGCGGCTGATCACCCCTGACGGCTCCATGCTGTTTAGAGTGACC ATCAACTCCTAATGA
SEQ ID NO: 53	α-HER3 light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGCTCTTACGAGTTGACACAGGACCCTGCTGTGTCTGTGGCTCTGGG ACAGACAGTGCGGATTACCTGTCAGGGCGACTCCCTGAGATCCTACTACGCC TCCTGGTATCAGCAGAAGCCTGGACAGGCTCCCGTGCTGGTCATCTACGGCA AGAACAACAGACCCTCTGGCATCCCTGACCGGTTCTCTGGCTCTACCTCTGG CAATTCCGCCAGCCTGACAATTACTGGCGCTCAGGCTGAGGACGAGGCCGAC TACTACTGCAACTCTAGAGACTCCCCTGGCAACCAGTGGGTGTTCGGCGGAG GAACAAAAGTGACAGTGCTCGGCGGCCAGCCTAAGGCCAATCCTACAGTGAC CCTGTTTCCTCCATCCTCCGAGGAACTGCAGGCCAACAAGGCTACCCTCGTG TGCCTGATCTCTGACTTTTACCCTGGCGCTGTGACCGTGGCTTGGAAGGCTG ATGGATCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCTAGCAAGCAGTC CAACAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAGTGG AAGTCCCACCGGTCCTACTCTTGCCAAGTGACCCATGAGGGCTCCACCGTGG AAAAGACAGTGGCCCCTACCGAGTGCTCTGGATCTTCTGGTGGCGGAGGATC TGGCGGAGGTGGAAGTAGTGGCGGCGTGACCGGCTACAGACTGTTCGAAGAG ATCCTGTAATGA
SEQ ID NO: 54	α-HER3 light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGCT CTACCGGCTCTTACGAGCTGACACAGGACCCTGCTGTGTCTGTGGCTCTGGG CCAGACAGTGCGGATTACCTGTCAGGGCGACTCCCTGAGATCCTACTACGCC TCCTGGTATCAGCAGAAGCCTGGACAGGCTCCCGTGCTGGTCATCTACGGCA AGAACAACCGGCCTAGCGGCATCCCTGACAGATTCTCCGGCTCTACCTCCGG CAACTCTGCCAGCCTGACAATTACTGGCGCCCAGGCTGAGGACGAGGCCGAC TACTACTGCAACTCCAGAGACTCCCCTGGCAACCAGTGGGTTTTCGGCGGAG GCACCAAAGTGACAGTGCTCGGAGGACAGCCCAAGGCCAATCCTACCGTGAC ACTGTTCCCTCCATCCTCCGAGGAACTGCAGGCCAACAAGGCTACCCTCGTG TGCCTGATCTCCGACTTTTACCCTGGCGCTGTGACCGTGGCCTGGAAGGCTG ATGGATCTCCTGTGAAGGCTGGCGTGGAAACCACCAAGCCTTCCAAGCAGTC CAACAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAGTGG AAGTCCCACCGGTCCTACAGCTGCCAAGTGACCCATGAGGGCTCCACCGTGG AAAAGACCGTGGCTCCTACCGAGTGCTCCTGATGA
SEQ ID NO: 55	α-TRAILR2 heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAAGTGCAGTTGGTTCAGTCTGGCGGCGGAGTTGAAAGACCTGG CGGATCTCTGAGACTGTCTTGTGCCGCCTCTGGCTTCACCTTCGACGACTAT GGCATGTCCTGGGTCCGACAGGCTCCTGGCAAAGGATTGGAATGGGTGTCCG GCATCAACTGGAATGGCGGCTCTACCGGCTACGCCGATTCTGTGAAGGGCAG AGTGACCATCTCTCGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAAC AGCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTGCTAAGATCCTCGGCG CTGGCAGAGGCTGGTATTTCGATCTGTGGGGCAAGGGCACCACCGTGACAGT GTCCTCTGCTTCTACCAAGGGACCCAGCGTTTTCCCTCTGGCTCCATCCTCT AAGTCCACCTCTGGTGGAACCGCTGCTCTGGGCTGTCTGGTCAAGGATTACT TCCCTGAGCCTGTGACCGTGTCCTGGAACTCTGGTGCTCTGACATCCGGCGT GCACACCTTTCCAGCTGTGCTGCAGTCCTCTGGCCTGTACTCTCTGTCCTCT GTCGTGACCGTGCCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAACG TGAACCACAAGCCTTCCAACACCAAAGTGGACAAGAGAGTGGAACCCAAGTC CTGCGGATCTTCTGGTGGCGGAGGATCTGGCGGAGGTGGAAGTAGTGGCGGA GTGTTCACCCTGGAAGATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATA

		ATCTGGACCAGGTTCTGGAACAAGGCGGCGTGTCCTCTCTGCTGCAGAATCT GGCTGTGTCTGTGACCCCTATCCAGAGAATCGTGCGCTCTGGCGAGAACGCC CTGAAGATCGACATCCACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATC AGATGGCTCAGATCGAAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCA CCACTTCAAAGTGATCCTGCCTTACGGCACCCTGGTCATCGATGGCGTGACC CCAAACATGCTGAACTACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCG ACGGCAAGAAAATCACCGTGACCGGCACACTGTGGAACGGCAACAAGATCAT CGACGAGCGGCTGATCACCCCTGACGGCTCCATGCTGTTTCGCGTGACCATC AACTCCTAATGA
SEQ ID NO: 56	α-TRAILR2 light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGATCCTCTGAGTTGACACAGGACCCTGCTGTGTCTGTGGCTCTGGG ACAGACAGTGCGGATTACCTGTCAGGGCGACTCCCTGAGATCCTACTACGCC TCCTGGTATCAGCAGAAGCCTGGACAGGCTCCCGTGCTGGTCATCTACGGCA AGAACAACAGACCCTCTGGCATCCCTGACCGGTTCTCCGGATCTAGCTCTGG CAATACCGCCAGCCTGACAATTACTGGCGCTCAGGCTGAGGACGAGGCCGAC TACTACTGCAACTCCAGAGACTCTTCCGGCAATCACGTGGTGTTTGGCGGCG GAACAAAGCTGACAGTGCTGGGCCAGCCTAAGGCCAATCCTACCGTGACACT GTTCCCTCCATCCTCCGAGGAACTGCAGGCTAACAAGGCTACCCTCGTGTGC CTGATCTCCGATTTTTACCCTGGCGCTGTGACCGTGGCTTGGAAGGCTGATG GATCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCTAGCAAGCAGTCCAA CAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAGTGGAAG TCCCACCGGTCCTACTCTTGCCAAGTGACCCATGAGGGCTCCACCGTGGAAA AGACAGTGGCCCCTACCGAGTGCTCTGGATCTTCTGGTGGCGGAGGATCTGG CGGAGGTGGAAGTAGTGGCGGCGTGACCGGCTACAGACTGTTCGAAGAGATC CTGTAATGA
SEQ ID NO: 57	α-TRAILR2 light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGCT CTACCGGATCCTCTGAGCTGACACAGGACCCTGCTGTGTCTGTGGCTCTGGG CCAGACAGTGCGGATTACCTGTCAGGGCGACTCCCTGAGATCCTACTACGCC TCCTGGTATCAGCAGAAGCCTGGACAGGCTCCCGTGCTGGTCATCTACGGCA AGAACAACCGGCCTAGCGGCATCCCTGACAGATTCTCCGGATCTTCCAGCGG CAATACCGCCAGCCTGACAATTACTGGCGCCCAGGCTGAGGACGAGGCCGAC TACTACTGCAACTCCAGAGACTCCTCCGGCAATCACGTGGTGTTTGGCGGCG GAACAAAGCTGACAGTGCTGGGCCAGCCTAAGGCCAATCCTACCGTGACACT GTTCCCTCCATCCTCCGAGGAACTGCAGGCCAACAAGGCTACCCTCGTGTGC CTGATCTCCGACTTTTACCCTGGCGCTGTGACCGTGGCCTGGAAGGCTGATG GATCTCCTGTGAAGGCTGGCGTGGAAACCACCAAGCCTTCCAAGCAGTCCAA CAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAGTGGAAG TCCCACCGGTCCTACAGCTGCCAAGTGACCCATGAGGGCTCCACCGTGGAAA AGACCGTGGCTCCTACCGAGTGCTCCTGATGA
SEQ ID NO: 58	α-activin receptors heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGTTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCTGG CGCTTCTGTGAAGGTGTCCTGCAAGGCCTCTGGCTACACCTTTACCTCCAGC TACATCAACTGGGTCCGACAGGCTCCTGGACAGGGACTTGAGTGGATGGGCA CCATCAATCCTGTGTCCGGCTCTACCAGCTACGCCCAGAAATTCCAGGGCAG AGTGACCATGACCAGAGACACCTCCATCTCCACCGCCTACATGGAACTGTCC CGGCTGAGATCTGACGACACCGCCGTGTACTATTGTGCCAGAGGCGGATGGT TCGATTACTGGGGACAGGGCACACTGGTCACCGTGTCCTCTGCTTCTACCAA GGGACCCTCTGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACCTCTGGTGGA ACCGCTGCTCTGGGCTGCCTGGTCAAGGATTACTTTCCTGAGCCTGTGACCG TGTCTTGGAACTCTGGTGCTCTGACCTCCGGCGTGCACACATTTCCAGCTGT GCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCTTCT

		AGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCTTCCA ACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCTTGCGGATCTTCTGGTGG CGGAGGATCTGGCGGAGGTGGAAGTAGTGGCGGAGTGTTCACCCTGGAAGAT TTCGTCGGCGATTGGGAGCAGACCGCCGCCTATAATCTGGACCAGGTTCTGG AACAAGGCGGCGTCAGCTCTCTGCTGCAGAATCTGGCTGTGTCTGTGACCCC TATCCAGAGAATTGTGCGCTCTGGCGAGAACGCCCTGAAGATCGACATCCAC GTGATCATCCCTTACGAGGGCCTGTCTGCCGATCAGATGGCTCAGATCGAAG AGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTTCAAAGTGATCCT GCCTTACGGCACCCTGGTCATCGATGGCGTGACCCCAAACATGCTGAACTAC TTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCAAGAAAATCACCG TGACCGGCACACTGTGGAACGGCAACAAGATCATCGACGAGCGGCTGATCAC CCCTGACGGCTCTATGCTGTTCCGCGTGACCATCAACTCCTAATGA
SEQ ID NO: 59	α-activin receptors light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACAGGCCAGTCTGCTTTGACTCAGCCTGCCTCTGTGTCTGGCTCCCCTGG CCAGTCTATCACCATCTCTTGTACCGGCACCTCCTCCGACGTGGGCTCCTAC AACTACGTGAACTGGTATCAGCAGCACCCCGGCAAGGCCCCTAAGCTGATGA TCTACGGCGTGTCCAAACGGCCCAGCGGAGTGTCTAACAGATTCTCCGGCTC CAAGTCTGGCAACACCGCTTCTCTGACAATCAGCGGACTGCAGGCCGAGGAC GAGGCTGATTACTACTGTGGCACCTTCGCTGGCGGCTCCTACTATGGTGTTT TTGGCGGCGGAACAAAGCTGACCGTGCTGGGCCAACCTAAGGCCAATCCTAC CGTGACACTGTTCCCTCCATCCTCCGAGGAACTGCAGGCTAACAAGGCTACC CTCGTGTGCCTGATCTCCGATTTTTACCCTGGCGCTGTGACCGTGGCTTGGA AGGCTGATGGATCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCTAGCAA GCAGTCCAACAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAA CAGTGGAAGTCCCACCGGTCCTACTCTTGCCAAGTGACCCATGAGGGCTCCA CCGTGGAAAAGACAGTGGCCCCTACCGAGTGCTCTGGATCTTCTGGTGGCGG AGGATCTGGCGGAGGTGGAAGTAGTGGCGGCGTGACCGGCTACAGACTGTTC GAAGAGATCCTGTAATGA
SEQ ID NO: 60	α-activin receptors light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACAGGCCAGTCTGCTTTGACTCAGCCTGCCTCTGTGTCTGGCTCCCCTGG CCAGTCTATCACCATCTCTTGTACCGGCACCTCCTCCGACGTGGGCTCCTAC AACTACGTGAACTGGTATCAGCAGCACCCCGGCAAGGCCCCTAAGCTGATGA TCTACGGCGTGTCCAAACGGCCCAGCGGAGTGTCTAACAGATTCTCCGGCTC CAAGTCTGGCAACACCGCTTCTCTGACAATCAGCGGACTGCAGGCCGAGGAC GAGGCTGATTACTACTGTGGCACCTTCGCTGGCGGCTCCTACTATGGTGTTT TTGGCGGCGGAACAAAGCTGACCGTGCTGGGCCAACCTAAGGCCAATCCTAC CGTGACACTGTTCCCTCCATCCTCCGAGGAACTGCAGGCTAACAAGGCTACC CTCGTGTGCCTGATCTCCGATTTTTACCCTGGCGCTGTGACCGTGGCTTGGA AGGCTGATGGATCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCTAGCAA GCAGTCCAACAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAA CAGTGGAAGTCCCACCGGTCCTACTCTTGCCAAGTGACCCATGAGGGCTCCA CCGTGGAAAAGACAGTGGCCCCTACCGAGTGCTCTTAATGA
SEQ ID NO: 61	α-complement C5 heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAAGTGCAGTTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCTGG CTCCTCTGTGAAGGTGTCCTGCAAGGCTTCTGGCGGCACCTTCTCCTCTTAC GCCATCTCTTGGGTCCGACAGGCTCCTGGACAAGGCTTGGAGTGGATGGGCG GCATCGGCCCTTTTTTCGGCACCGCCAACTACGCCCAGAAATTCCAGGGCAG AGTGACCATCACCGCCGACGAGTCTACCTCCACCGCTTACATGGAACTGTCC AGCCTGAGATCTGAGGACACCGCCGTGTACTACTGCGCCAGAGACACCCCTT ACTTCGATTATTGGGGCCAGGGCACCCTGGTCACCGTGTCCTCTGCTTCTAC AAAGGGCCCCTCTGTGTTCCCTCTGGCTCCTAGCTCTAAGTCTACATCTGGC

		GGAACCGCTGCTCTGGGCTGCCTGGTCAAGGATTACTTTCCTGAGCCTGTGA CCGTGTCTTGGAACTCTGGTGCTCTGACCTCCGGCGTGCACACATTTCCAGC TGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCT TCTAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCTT CCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCTTGCGGATCTTCCGG TGGCGGAGGAAGCGGAGGCGGAGGATCTAGTGGCGGAGTGTTCACCCTGGAA GATTTCGTCGGCGATTGGGAGCAGACCGCCGCCTATAATCTGGACCAGGTTC TGGAACAAGGCGGGGTGTCCTCTCTGCTGCAGAATCTGGCTGTGTCTGTGAC CCCTATCCAGAGAATCGTGCGCTCTGGCGAGAACGCCCTGAAGATCGACATC CACGTGATCATCCCTTACGAGGGCCTGTCTGCCGATCAGATGGCTCAGATCG AAGAGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTTCAAAGTGAT CCTGCCTTACGGCACCCTCGTGATCGATGGCGTGACCCCAAACATGCTGAAC TACTTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCAAGAAAATCA CCGTGACCGGCACACTGTGGAACGGCAACAAGATCATCGACGAGCGGCTGAT CACCCCTGACGGCTCTATGCTGTTTAGAGTGACAATCAACTCCTAATGA
SEQ ID NO: 62	α-complement C5 light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGCTCTTATGAGCTGACACAGCCTCTGTCTGTGTCTGTGGCTCTGGG CCAGACCGCCAGAATCACCTGTTCTGGCGACAGCATCCCCAACTACTACGTG TACTGGTATCAGCAGAAGCCCGGCCAGGCTCCTGTGCTGGTCATCTACGACG ACTCCAACAGACCCAGCGGCATCCCTGAGAGATTCTCCGGCTCTAACTCTGG CAACACCGCCACACTGACCATCTCTAGAGCACAGGCTGGCGACGAGGCCGAC TACTACTGCCAGTCTTTCGACAGCTCTCTGAACGCCGAAGTGTTCGGCGGAG GCACAAAACTGACAGTGCTGGGCCAGCCTAAGGCCAATCCTACCGTGACACT GTTCCCTCCATCCTCCGAGGAACTGCAGGCTAACAAGGCTACCCTCGTGTGC CTGATCTCCGATTTTTACCCTGGCGCTGTGACCGTGGCTTGGAAGGCTGATG GATCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCTAGCAAGCAGTCCAA CAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAGTGGAAG TCCCACCGGTCCTACTCTTGCCAAGTGACCCATGAGGGCTCCACCGTGGAAA AGACAGTGGCCCCTACCGAGTGCTCTGGATCTTCTGGTGGCGGAGGATCTGG CGGAGGTGGAAGTAGTGGCGGCGTGACCGGCTACAGACTGTTCGAAGAGATC CTGTAATGA
SEQ ID NO: 63	α-complement C5 light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGCT CTACCGGCTCTTATGAGCTGACACAGCCTCTGTCTGTGTCTGTGGCTCTGGG CCAGACCGCCAGAATCACCTGTTCTGGCGACAGCATCCCCAACTACTACGTG TACTGGTATCAGCAGAAGCCCGGCCAGGCTCCTGTGCTGGTCATCTACGACG ACTCCAACAGACCCAGCGGCATCCCTGAGAGATTCTCCGGCTCTAACTCTGG CAACACCGCCACACTGACCATCTCTAGAGCACAGGCTGGCGACGAGGCCGAC TACTACTGCCAGTCTTTCGACAGCTCTCTGAACGCCGAAGTGTTCGGCGGAG GCACAAAACTGACAGTGCTGGGCCAGCCTAAGGCCAATCCTACCGTGACACT GTTCCCTCCATCCTCCGAGGAACTGCAGGCTAACAAGGCTACCCTCGTGTGC CTGATCTCCGATTTTTACCCTGGCGCTGTGACCGTGGCTTGGAAGGCTGATG GATCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCTAGCAAGCAGTCCAA CAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAGTGGAAG TCCCACCGGTCCTACTCTTGCCAAGTGACCCATGAGGGCTCCACCGTGGAAA AGACAGTGGCCCCTACCGAGTGCTCTTAATGA
SEQ ID NO: 64	α-CCR2 heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAAGTGCAGTTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCTGG CGCTTCTGTGAAGGTGTCCTGCAAGGCCTCTGGCTACACCTTTACCGGCTAC CACATGCACTGGGTCCGACAGGCTCCAGGACAAGGATTGGAGTGGATGGGCT GGATCAACCCCAACTCCGGCGTGACCAAATACGCCCAGAAATTCCAGGGCAG AGTGACCATGACCAGAGACACCTCCATCAACACCGCCTACATGGAACTGTCC

		CGGCTGAGATTCGACGACACCGACGTGTACTATTGTGCCACCGGCGGCTTTG GCTATTGGGGAGAGGGAACACTGGTCACCGTGTCCTCTGCTTCTACCAAGGG ACCCTCCGTGTTTCCTCTGGCTCCTTCCAGCAAGTCTACCTCTGGTGGAACC GCTGCTCTGGGCTGCCTGGTCAAGGATTACTTTCCTGAGCCTGTGACCGTGT CTTGGAACTCTGGTGCTCTGACCAGCGGCGTGCACACATTTCCAGCTGTGCT GCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCTTCTAGC TCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCTTCCAACA CCAAGGTGGACAAGAGAGTGGAACCCAAGTCTTGCGGATCTTCTGGTGGCGG AGGATCTGGCGGAGGTGGAAGTAGTGGCGGAGTGTTCACCCTGGAAGATTTC GTCGGCGATTGGGAGCAGACCGCCGCCTATAATCTGGACCAGGTTCTGGAAC AAGGCGGCGTCAGCTCTCTGCTGCAGAATCTGGCTGTGTCTGTGACCCCTAT CCAGAGAATCGTGCGCTCTGGCGAGAACGCCCTGAAGATCGACATCCACGTG ATCATCCCTTACGAGGGCCTGTCTGCCGATCAGATGGCTCAGATCGAAGAGG TGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTTCAAAGTGATCCTGCC TTACGGCACCCTGGTCATCGATGGCGTGACCCCAAACATGCTGAACTACTTC GGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCAAGAAAATCACCGTGA CCGGCACACTGTGGAACGGCAACAAGATCATCGACGAGCGGCTGATCACCCC TGACGGCTCTATGCTGTTCCGCGTGACCATCAACTCCTAATGA
SEQ ID NO: 65	α-CCR2 light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCCTGCCTGTTCTGACACAGCCTCCTAGCGTGTCCAAGGGCCTGAG ACAGACCGCTACACTGACCTGCACCGGCAACTCTAACAACGTGGGAAATCAG GGCGCTGCCTGGTTGCAGCAGCATCAGGGACAACCTCCAAAGCTGCTGTCCT ACCGGAACCACAATAGACCTTCCGGCGTGTCCGAGCGGTTCAGCCCTTCTAG ATCTGGCGACACCTCTAGCCTGACCATCACTGGACTGCAGCCTGAGGACGAG GCCGATTACTACTGTCTGGCCTGGGATTCTTCTCTGCGGGCCTTTGTGTTTG GCACCGGCACAAAACTGACCGTGCTGGGCCAGCCTAAGGCCAATCCTACAGT GACCCTGTTTCCTCCATCCTCCGAGGAACTGCAGGCCAACAAGGCTACCCTC GTGTGCCTGATCTCTGACTTTTACCCTGGCGCTGTGACCGTGGCTTGGAAGG CTGATGGATCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCTAGCAAGCA GTCCAACAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAG TGGAAGTCCCACCGGTCCTACTCTTGCCAAGTGACCCATGAGGGCTCCACCG TGGAAAAGACAGTGGCCCCTACCGAGTGCTCTGGATCTTCTGGTGGCGGAGG ATCTGGCGGAGGTGGAAGTAGTGGCGGCGTGACCGGCTACAGACTGTTCGAA GAGATCCTGTAATGA
SEQ ID NO: 66	α-CCR2 light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGACTGCCCGTGTTGACCCAGCCTCCTAGCGTTTCCAAGGGCCTGAG ACAGACCGCCACACTGACCTGTACCGGCAACTCTAACAACGTGGGCAATCAG GGCGCTGCCTGGTTGCAGCAGCATCAGGGACAGCCTCCAAAGCTGCTGTCCT ACCGGAACCACAACAGACCTAGCGGCGTGTCCGAGCGGTTCAGCCCTTCTAG ATCTGGCGACACCTCCAGCCTGACCATCACTGGACTGCAGCCTGAGGACGAG GCCGACTACTATTGTCTGGCCTGGGACAGCTCCCTGCGGGCCTTTGTTTTTG GCACCGGCACCAAGCTGACCGTGCTGGGACAACCTAAGGCCAATCCTACCGT GACACTGTTCCCTCCATCCTCCGAGGAACTGCAGGCCAACAAGGCTACCCTC GTGTGCCTGATCTCCGACTTTTACCCTGGCGCTGTGACCGTGGCCTGGAAGG CTGATGGATCTCCTGTGAAGGCTGGCGTGGAAACCACCAAGCCTTCCAAGCA GTCCAACAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAG TGGAAGTCCCACCGGTCCTACAGCTGCCAAGTGACCCATGAGGGCTCCACCG TGGAAAAGACCGTGGCTCCTACCGAGTGCTCCTGATGA
SEQ ID NO:	α-CCR2 heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCGAGGTGCAGTTGGTTGAATCTGGCGGAGGATTGGTGCAGCCTGG CGGATCTCTGAGACTGTCTTGTGTGGCCTCCGGCTTCACCTTCTCCGACTAC

67		TGGATGTCCTGGGTCCGACAGGCTCCTGGCAAAGGACTGGAATGGGTCGCCA ACATCAAGAAAGACGGCTCCGTGAACTACTACGTGGACTCCGTGAAGGGCAG ATTCACCATCTCTCGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAAC AGCCTGAGAGCCGAGGACACCGCCGTGTACTACTGCACCAGATTCGATTATT GGGGCCAGGGCACCCTGGTCACCGTGTCCTCTGCTTCTACAAAGGGCCCCTC TGTGTTCCCTCTGGCTCCTTCCTCTAAATCCACCTCTGGCGGAACCGCTGCT CTGGGCTGTCTGGTCAAGGATTACTTCCCTGAGCCTGTGACCGTGTCTTGGA ACTCTGGTGCTCTGACATCCGGCGTGCACACCTTTCCAGCTGTGCTGCAGTC CTCTGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCTTCTAGCTCTCTG GGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCTTCCAACACCAAGG TGGACAAGAGAGTGGAACCCAAGTCTTGCGGATCTTCTGGTGGTGGTGGAAG TGGCGGAGGCGGTTCTTCAGGCGGAGTGTTCACCCTGGAAGATTTCGTCGGC GATTGGGAGCAGACCGCCGCCTATAATCTGGACCAGGTTCTGGAACAAGGCG GCGTCAGCTCTCTGCTGCAGAATCTGGCTGTGTCTGTGACCCCTATCCAGAG AATCGTGCGCTCTGGCGAGAACGCCCTGAAGATCGACATCCACGTGATCATC CCTTACGAGGGCCTGTCTGCCGATCAGATGGCTCAGATCGAAGAGGTGTTCA AGGTGGTGTACCCCGTGGACGACCACCACTTCAAAGTGATCCTGCCTTACGG CACCCTCGTGATCGATGGCGTGACCCCAAACATGCTGAACTACTTCGGCAGA CCCTACGAGGGAATCGCCGTGTTCGACGGCAAGAAAATCACCGTGACCGGCA CACTGTGGAACGGCAACAAGATCATCGACGAGCGGCTGATCACCCCTGACGG CTCCATGCTGTTTAGAGTGACCATCAACTCCTAATGA
SEQ ID NO: 68	α-CCR2 light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGTTGTTGTGGGTGCCAGGAT CTACAGGCCAGGCTGGATTGACACAGCCTCCTAGCGTGTCCAAGGGCCTGAG ACAGACCGCTACACTGACCTGCACCGGCAACTCTAACAACGTGGGAAATCAG GGCGCTGCCTGGTTGCAGCAGCATCAGGGACATCCTCCAAAGCTGCTGTTCT ACCGGAACAACAATAGAGCCTCCGGCATCTCCGAGCGGCTGTCTGCTTCTAG ATCTGGCAATACCGCCAGCCTGACCATCACTGGACTGCAGCCTGAGGACGAG GCCGACTACTATTGCCTGACCTGGGACTCCTCTCTGTCCGTGGTTGTGTTTG GCGGCGGAACAAAGCTGACAGTGCTGGGCCAGCCTAAGGCCAATCCTACCGT GACACTGTTCCCTCCATCCTCCGAGGAACTGCAGGCTAACAAGGCTACCCTC GTGTGCCTGATCTCCGATTTTTACCCTGGCGCTGTGACCGTGGCTTGGAAGG CTGATGGATCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCTAGCAAGCA GTCCAACAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAG TGGAAGTCCCACCGGTCCTACTCTTGCCAAGTGACCCATGAGGGCTCCACCG TGGAAAAGACAGTGGCCCCTACCGAGTGCTCTGGATCTTCTGGTGGCGGAGG ATCTGGCGGAGGTGGAAGTAGTGGCGGCGTGACCGGCTACAGACTGTTCGAA GAGATCCTGTAATGA
SEQ ID NO: 69	α-CCR2 light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGACAGGCTGGCTTGACCCAGCCTCCTAGCGTTTCCAAGGGCCTGAG ACAGACCGCCACACTGACCTGTACCGGCAACTCTAACAACGTGGGCAATCAG GGCGCTGCCTGGTTGCAGCAGCATCAGGGACATCCTCCAAAGCTGCTGTTCT ACCGGAACAACAACAGAGCCTCCGGCATCTCCGAGCGGCTGTCTGCTTCTAG ATCCGGCAATACCGCCAGCCTGACCATCACTGGACTGCAGCCTGAGGACGAG GCCGACTACTATTGCCTGACCTGGGACTCCTCTCTGTCCGTGGTGGTTTTTG GCGGAGGCACCAAGCTGACAGTGCTGGGACAGCCTAAGGCCAATCCTACCGT GACACTGTTCCCTCCATCCTCCGAGGAACTGCAGGCCAACAAGGCTACCCTC GTGTGCCTGATCTCCGACTTTTACCCTGGCGCTGTGACCGTGGCCTGGAAGG CTGATGGATCTCCTGTGAAGGCTGGCGTGGAAACCACCAAGCCTTCCAAGCA GTCCAACAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAG TGGAAGTCCCACCGGTCCTACAGCTGCCAAGTGACCCATGAGGGCTCCACCG TGGAAAAGACCGTGGCTCCTACCGAGTGCTCCTGATGA

SEQ ID NO: 70	α-IL12β heavy - LgBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGCTGGTGGAATCTGGTGGCGGAGTTGTGCAGCCTGG CAGATCCCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCTCTTAC GGAATGCACTGGGTCCGACAGGCCCCTGGCAAAGGATTGGAGTGGGTCGCCT TCATCAGATACGACGGCTCCAACAAGTACTACGCCGACTCCGTGAAGGGCAG ATTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGAGAGCCGAGGACACCGCCGTGTACTACTGCAAGACCCACGGCTCTC ACGACAATTGGGGCCAGGGCACAATGGTCACCGTGTCCTCTGCTTCCACCAA GGGACCCTCTGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACCTCTGGCGGA ACAGCTGCTCTGGGCTGCCTGGTCAAGGACTACTTTCCTGAGCCTGTGACCG TGTCTTGGAACTCTGGCGCTCTGACATCCGGCGTGCACACCTTTCCAGCTGT GCTGCAATCCTCCGGCCTGTACTCTCTGTCCTCCGTCGTGACCGTGCCTTCT AGCTCTCTGGGCACCCAGACCTACATCTGCAATGTGAACCACAAGCCTTCCA ACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCCTGCGGATCTTCTGGCGG CGGAGGATCTGGCGGAGGTGGTAGTTCAGGCGGAGTGTTCACCCTGGAAGAT TTCGTCGGCGACTGGGAGCAGACCGCCGCCTATAATCTGGACCAGGTGCTGG AACAAGGCGGCGTCAGTTCTCTGCTGCAGAACCTGGCTGTGTCTGTGACCCC TATCCAGAGAATCGTGCGGAGCGGCGAGAACGCCCTGAAGATCGATATCCAC GTGATCATCCCTTACGAGGGCCTGAGCGCCGATCAGATGGCTCAGATCGAAG AGGTGTTCAAGGTGGTGTACCCCGTGGACGACCACCACTTCAAAGTGATCCT GCCTTACGGCACCCTGGTCATCGATGGCGTGACCCCAAACATGCTGAACTAC TTCGGCAGACCCTACGAGGGAATCGCCGTGTTCGACGGCAAGAAAATCACCG TGACCGGCACACTGTGGAACGGCAACAAGATCATCGACGAGCGGCTGATCAC CCCTGACGGCTCTATGCTGTTCAGAGTGACCATCAACAGCTGATGA
SEQ ID NO: 71	α-IL12β light - SmBiT	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACCGGACAGTCCGTGTTGACCCAGCCTCCTTCTGTTTCTGGCGCTCCTGG CCAGAGAGTGACCATCTCTTGCTCCGGCTCTCGGTCCAACATCGGCTCCAAT ACCGTGAAGTGGTATCAGCAGCTGCCCGGCACAGCTCCCAAACTGCTGATCT ACTACAACGACCAGCGGCCTTCTGGCGTGCCCGATAGATTCTCTGGCTCCAA GTCTGGCACCTCTGCCAGCCTGGCTATTACCGGACTGCAGGCTGAGGACGAG GCCGACTACTACTGCCAGTCTTACGACCGGTACACCCATCCTGCTCTGCTGT TTGGCACCGGCACCAAAGTGACAGTGCTGGGCCAGCCTAAGGCCAATCCTAC CGTGACACTGTTCCCTCCATCCTCCGAAGAACTGCAGGCCAACAAGGCTACC CTCGTGTGCCTGATCTCCGACTTTTACCCTGGCGCTGTGACCGTGGCCTGGA AGGCTGATGGATCTCCTGTGAAGGCTGGCGTGGAAACCACCAAGCCTTCCAA GCAGTCCAACAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAA CAGTGGAAGTCCCACCGGTCCTACAGCTGCCAAGTGACCCATGAGGGCTCCA CCGTGGAAAAGACCGTGGCTCCTACCGAGTGCTCCGGATCTTCTGGTGGCGG AGGATCTGGCGGAGGCGGTTCTTCAGGCGGAGTGACCGGCTACAGACTGTTC GAAGAGATCCTGTGATGA
SEQ ID NO: 72	α-IL12β light	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACCGGACAGTCCGTGTTGACCCAGCCTCCTTCTGTTTCTGGCGCTCCTGG CCAGAGAGTGACCATCTCTTGCTCCGGCTCTCGGTCCAACATCGGCTCCAAT ACCGTGAAGTGGTATCAGCAGCTGCCCGGCACAGCTCCCAAACTGCTGATCT ACTACAACGACCAGCGGCCTTCTGGCGTGCCCGATAGATTCTCTGGCTCCAA GTCTGGCACCTCTGCCAGCCTGGCTATTACCGGACTGCAGGCTGAGGACGAG GCCGACTACTACTGCCAGTCTTACGACCGGTACACCCATCCTGCTCTGCTGT TTGGCACCGGCACCAAAGTGACAGTGCTGGGCCAGCCTAAGGCCAATCCTAC CGTGACACTGTTCCCTCCATCCTCCGAAGAACTGCAGGCCAACAAGGCTACC CTCGTGTGCCTGATCTCCGACTTTTACCCTGGCGCTGTGACCGTGGCCTGGA AGGCTGATGGATCTCCTGTGAAGGCTGGCGTGGAAACCACCAAGCCTTCCAA

		GCAGTCCAACAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAA CAGTGGAAGTCCCACCGGTCCTACAGCTGCCAAGTGACCCATGAGGGCTCCA CCGTGGAAAAGACCGTGGCTCCTACCGAGTGCTCCTGATGA
SEQ ID NO: 73	α-CTLA4 heavy - hCHIg	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGCTGGTGGAATCTGGTGGCGGAGTTGTGCAGCCTGG CAGATCCCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCAGCTAC ACCATGCACTGGGTCCGACAGGCCCCTGGCAAAGGATTGGAGTGGGTCACCT TCATCTCTTACGACGGCAACAACAAGTACTACGCCGACTCCGTGAAGGGCAG ATTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGAGAGCCGAGGACACCGCCATCTACTACTGTGCTAGAACCGGCTGGC TGGGCCCCTTTGATTATTGGGGACAGGGCACCCTGGTCACCGTGTCCTCTGC TTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACC TCTGGCGGAACAGCTGCTCTGGGCTGCCTGGTCAAGGACTACTTTCCTGAGC CTGTGACCGTGTCTTGGAACTCTGGCGCTCTGACATCCGGCGTGCACACATT TCCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACC GTGCCTTCCAGCTCTCTGGGAACCCAGACCTACATCTGCAATGTGAACCACA AGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCCTGCGACAA GACCCACACCTGTCCACCATGTCCTGCTCCAGAACTGCTCGGCGGACCTTCC GTGTTCCTGTTTCCTCCAAAGCCTAAGGACACCCTGATGATCTCTCGGACCC CTGAAGTGACCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCGAAGTGAA GTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCT AGAGAGGAACAGTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGC TGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAA GGCCCTGCCTGCTCCTATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCT AGGGAACCCCAGGTTTACACCCTGCCTCCAAGCCGGGAAGAGATGACCAAGA ACCAGGTGTCCCTGACCTGCCTCGTGAAGGGATTCTACCCCTCCGATATCGC CGTGGAATGGGAGTCTAATGGCCAGCCTGAGAACAACTACAAGACAACCCCT CCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACTCCAAGCTGACAGTGG ACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGA GGCCCTGCACAATCACTACACCCAGAAGTCCCTGTCTCTGAGCCCCGGCAAG TGATGA
SEQ ID NO: 74	α-IL12β heavy - hCHIg	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGCTGGTGGAATCTGGTGGCGGAGTTGTGCAGCCTGG CAGATCCCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCTCTTAC GGAATGCACTGGGTCCGACAGGCCCCTGGCAAAGGATTGGAGTGGGTCGCCT TCATCAGATACGACGGCTCCAACAAGTACTACGCCGACTCCGTGAAGGGCAG ATTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGAGAGCCGAGGACACCGCCGTGTACTACTGCAAGACCCACGGCTCTC ACGACAATTGGGGCCAGGGCACAATGGTCACCGTGTCCTCTGCTTCCACCAA GGGACCCTCTGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACCTCTGGCGGA ACAGCTGCTCTGGGCTGCCTGGTCAAGGACTACTTTCCTGAGCCTGTGACCG TGTCTTGGAACTCTGGCGCTCTGACATCCGGCGTGCACACCTTTCCAGCTGT GCTGCAATCCTCCGGCCTGTACTCTCTGTCCTCCGTCGTGACCGTGCCTTCT AGCTCTCTGGGCACCCAGACCTACATCTGCAATGTGAACCACAAGCCTTCCA ACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCCTGCGATAAGACCCACAC CTGTCCACCATGTCCTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCCTG TTTCCTCCAAAGCCTAAGGACACCCTGATGATCTCTCGGACCCCTGAAGTGA CCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCGAAGTGAAGTTCAATTG GTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAA CAGTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGG ATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCC

		TGCTCCTATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTAGGGAACCC CAGGTTTACACCCTGCCTCCAAGCCGGGAAGAGATGACCAAGAACCAGGTGT CCCTGACCTGCCTCGTGAAGGGATTCTACCCCTCCGATATCGCCGTGGAATG GGAGTCTAATGGCCAGCCTGAGAACAACTACAAGACCACACCTCCTGTGCTG GACTCCGACGGCTCATTCTTCCTGTACTCCAAGCTGACAGTGGACAAGTCCA GATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCA CAATCACTACACCCAGAAGTCCCTGTCTCTGAGCCCCGGCAAGTGATGA
SEQ ID NO: 75	α-IL12β light-hCLIg_vl - IL2	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACCGGACAGTCCGTGTTGACCCAGCCTCCTTCTGTTTCTGGCGCTCCTGG CCAGAGAGTGACCATCTCTTGCTCCGGCTCTCGGTCCAACATCGGCTCCAAT ACCGTGAAGTGGTATCAGCAGCTGCCCGGCACAGCTCCCAAACTGCTGATCT ACTACAACGACCAGCGGCCTTCTGGCGTGCCCGATAGATTCTCTGGCTCCAA GTCTGGCACCTCTGCCAGCCTGGCTATTACCGGACTGCAGGCTGAGGACGAG GCCGACTACTACTGCCAGTCTTACGACCGGTACACCCATCCTGCTCTGCTGT TTGGCACCGGCACCAAAGTGACAGTGCTGGGCCAGCCTAAGGCCAATCCTAC CGTGACACTGTTCCCTCCATCCTCCGAAGAACTGCAGGCCAACAAGGCTACC CTCGTGTGCCTGATCTCCGACTTTTACCCTGGCGCTGTGACCGTGGCCTGGA AGGCTGATGGATCTCCTGTGAAGGCTGGCGTGGAAACCACCAAGCCTTCCAA GCAGTCCAACAACAAATACGCCGCCTCCTCCTACCTGTCTCTGACCCCTGAA CAGTGGAAGTCCCACCGGTCCTACAGCTGCCAAGTGACCCATGAGGGCTCCA CCGTGGAAAAGACCGTGGCTCCTACAGAGTGTTCTGGCGGCGGAGGATCTGG CGGAGGTGGAAGCGGAGGCGGTGGATCTGCTCCTACCTCCTCCAGCACCAAG AAAACCCAGCTGCAGTTGGAGCATCTGCTGCTGGACCTGCAGATGATCCTGA ACGGCATCAACAACTACAAGAACCCCAAGCTGACCCGGATGCTGACCGCCAA GTTTGCCATGCCTAAGAAGGCCACCGAGCTGAAACATCTGCAGTGCCTGGAA GAGGAACTGAAGCCCCTGGAAGAAGTGCTGAATCTGGCCCAGTCCAAGAACT TCCACCTGAGGCCTCGGGACCTGATCAGCAACATCAACGTGATCGTGCTCGA GCTGAAGGGCTCCGAGACAACCTTCATGTGCGAGTACGCCGACGAGACAGCT ACCATCGTGGAATTTCTGAACCGGTGGATCACCTTCTGCCAGTCCATCATCA GCACCCTGACCTGATGA
SEQ ID NO: 76	α-IL12β heavy - hCHIg_Hole_Cys	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGCTGGTGGAATCTGGTGGCGGAGTTGTGCAGCCTGG CAGATCCCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCTCTTAC GGAATGCACTGGGTCCGACAGGCCCCTGGCAAAGGATTGGAGTGGGTCGCCT TCATCAGATACGACGGCTCCAACAAGTACTACGCCGACTCCGTGAAGGGCAG ATTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGAGAGCCGAGGACACCGCCGTGTACTACTGCAAGACCCACGGCTCTC ACGACAATTGGGGCCAGGGCACAATGGTCACCGTGTCCTCTGCTTCCACCAA GGGACCCTCTGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACCTCTGGCGGA ACAGCTGCTCTGGGCTGCCTGGTCAAGGACTACTTTCCTGAGCCTGTGACCG TGTCTTGGAACTCTGGCGCTCTGACATCCGGCGTGCACACCTTTCCAGCTGT GCTGCAATCCTCCGGCCTGTACTCTCTGTCCTCCGTCGTGACCGTGCCTTCT AGCTCTCTGGGCACCCAGACCTACATCTGCAATGTGAACCACAAGCCTTCCA ACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCCTGCGATAAGACCCACAC CTGTCCACCATGTCCTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCCTG TTTCCTCCAAAGCCTAAGGACACCCTGATGATCTCTCGGACCCCTGAAGTGA CCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCGAAGTGAAGTTCAATTG GTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAA CAGTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGG ATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCC TGCTCCTATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGGGAACCT

		CAAGTCTGTACCCTGCCTCCTAGCCGGGAAGAGATGACCAAGAACCAGGTGT CCCTGTCCTGCGCTGTGAAGGGCTTCTACCCTTCCGATATCGCCGTGGAATG GGAGAGCAATGGCCAGCCTGAGAACAACTACAAGACCACACCTCCTGTGCTG GACTCCGACGGCTCATTCTTCCTGGTGTCCAAGCTGACAGTGGACAAGTCCA GATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCA CAATCACTACACCCAGAAGTCCCTGTCTCTGTCTCCCGGAAAAGGCGGCGGA GGATCTGGCGGAGGTGGTAGCGGAGGCGGTGGATCTGCTCCTACCTCCTCCA GCACCAAGAAAACCCAGCTGCAGTTGGAGCATCTGCTGCTGGACCTCCAGAT GATCCTGAATGGCATCAACAATTACAAGAACCCCAAGCTCACCCGGATGCTG ACCGCCAAGTTTGCCATGCCTAAGAAGGCCACCGAGCTGAAACATCTGCAGT GCCTGGAAGAGGAACTGAAGCCCCTGGAAGAAGTGCTGAATCTGGCCCAGTC CAAGAACTTCCACCTGAGGCCTCGGGACCTGATCTCCAACATCAACGTGATC GTGCTCGAGCTGAAGGGCTCCGAGACAACCTTCATGTGCGAGTACGCCGACG AGACAGCTACCATCGTGGAATTTCTGAACCGGTGGATCACCTTCTGCCAGTC CATCATCAGCACCCTGACCTGATGA
SEQ ID NO: 77	α-IL12β heavy - hCHIg	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGCTGGTGGAATCTGGTGGCGGAGTTGTGCAGCCTGG CAGATCCCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCTCTTAC GGAATGCACTGGGTCCGACAGGCCCCTGGCAAAGGATTGGAGTGGGTCGCCT TCATCAGATACGACGGCTCCAACAAGTACTACGCCGACTCCGTGAAGGGCAG ATTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGAGAGCCGAGGACACCGCCGTGTACTACTGCAAGACCCACGGCTCTC ACGACAATTGGGGCCAGGGCACAATGGTCACCGTGTCCTCTGCTTCCACCAA GGGACCCTCTGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACCTCTGGCGGA ACAGCTGCTCTGGGCTGCCTGGTCAAGGACTACTTTCCTGAGCCTGTGACCG TGTCTTGGAACTCTGGCGCTCTGACATCCGGCGTGCACACCTTTCCAGCTGT GCTGCAATCCTCCGGCCTGTACTCTCTGTCCTCCGTCGTGACCGTGCCTTCT AGCTCTCTGGGCACCCAGACCTACATCTGCAATGTGAACCACAAGCCTTCCA ACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCCTGCGATAAGACCCACAC CTGTCCACCATGTCCTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCCTG TTTCCTCCAAAGCCTAAGGACACCCTGATGATCTCTCGGACCCCTGAAGTGA CCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCGAAGTGAAGTTCAATTG GTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAA CAGTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGG ATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCC TGCTCCTATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTAGGGAACCC CAGGTTTACACCCTGCCTCCAAGCCGGGAAGAGATGACCAAGAACCAGGTGT CCCTGACCTGCCTCGTGAAGGGATTCTACCCCTCCGATATCGCCGTGGAATG GGAGTCTAATGGCCAGCCTGAGAACAACTACAAGACCACACCTCCTGTGCTG GACTCCGACGGCTCATTCTTCCTGTACTCCAAGCTGACAGTGGACAAGTCCA GATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCA CAATCACTACACCCAGAAGTCCCTGTCTCTGTCTCCCGGAAAAGGCGGCGGA GGATCTGGCGGAGGTGGTAGCGGAGGCGGTGGATCTGCTCCTACCTCCTCCA GCACCAAGAAAACCCAGCTGCAGTTGGAGCATCTGCTGCTGGACCTCCAGAT GATCCTGAATGGCATCAACAATTACAAGAACCCCAAGCTCACCCGGATGCTG ACCGCCAAGTTTGCCATGCCTAAGAAGGCCACCGAGCTGAAACATCTGCAGT GCCTGGAAGAGGAACTGAAGCCCCTGGAAGAAGTGCTGAATCTGGCCCAGTC CAAGAACTTCCACCTGAGGCCTCGGGACCTGATCTCCAACATCAACGTGATC GTGCTCGAGCTGAAGGGCTCCGAGACAACCTTCATGTGCGAGTACGCCGACG AGACAGCTACCATCGTGGAATTTCTGAACCGGTGGATCACCTTCTGCCAGTC CATCATCTCCACACTGACCTGATGA

SEQ ID NO: 78	α-CTLA4 heavy - hCHIg_Knob_Cys	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGCTGGTGGAATCTGGTGGCGGAGTTGTGCAGCCTGG CAGATCCCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCAGCTAC ACCATGCACTGGGTCCGACAGGCCCCTGGCAAAGGATTGGAGTGGGTCACCT TCATCTCTTACGACGGCAACAACAAGTACTACGCCGACTCCGTGAAGGGCAG ATTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGAGAGCCGAGGACACCGCCATCTACTACTGTGCTAGAACCGGCTGGC TGGGCCCCTTTGATTATTGGGGACAGGGCACCCTGGTCACCGTGTCCTCTGC TTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACC TCTGGCGGAACAGCTGCTCTGGGCTGCCTGGTCAAGGACTACTTTCCTGAGC CTGTGACCGTGTCTTGGAACTCTGGCGCTCTGACATCCGGCGTGCACACATT TCCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACC GTGCCTTCCAGCTCTCTGGGAACCCAGACCTACATCTGCAATGTGAACCACA AGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCCTGCGACAA GACCCACACCTGTCCACCATGTCCTGCTCCAGAACTGCTCGGCGGACCTTCC GTGTTCCTGTTTCCTCCAAAGCCTAAGGACACCCTGATGATCTCTCGGACCC CTGAAGTGACCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCGAAGTGAA GTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCT AGAGAGGAACAGTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGC TGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAA GGCCCTGCCTGCTCCTATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCT AGGGAACCCCAGGTTTACACCCTGCCTCCATGCCGGGAAGAGATGACCAAGA ACCAGGTGTCCCTGTGGTGCCTGGTTAAGGGCTTCTACCCCTCCGATATCGC CGTGGAATGGGAGTCTAATGGCCAGCCTGAGAACAACTACAAGACAACCCCT CCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACTCCAAGCTGACAGTGG ACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGA GGCCCTGCACAATCACTACACCCAGAAGTCCCTGTCTCTGAGCCCCGGCAAG TGATGA
SEQ ID NO: 79	α-CTLA4 heavy - hCHIg_Knob_Cys - GH_scFv	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGCTGGTGGAATCTGGTGGCGGAGTTGTGCAGCCTGG CAGATCCCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCAGCTAC ACCATGCACTGGGTCCGACAGGCCCCTGGCAAAGGATTGGAGTGGGTCACCT TCATCTCTTACGACGGCAACAACAAGTACTACGCCGACTCCGTGAAGGGCAG ATTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGAGAGCCGAGGACACCGCCATCTACTACTGTGCTAGAACCGGCTGGC TGGGCCCCTTTGATTATTGGGGACAGGGCACCCTGGTCACCGTGTCCTCTGC TTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACC TCTGGCGGAACAGCTGCTCTGGGCTGCCTGGTCAAGGACTACTTTCCTGAGC CTGTGACCGTGTCTTGGAACTCTGGCGCTCTGACATCCGGCGTGCACACATT TCCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACC GTGCCTTCCAGCTCTCTGGGAACCCAGACCTACATCTGCAATGTGAACCACA AGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCCTGCGACAA GACCCACACCTGTCCACCATGTCCTGCTCCAGAACTGCTCGGCGGACCTTCC GTGTTCCTGTTTCCTCCAAAGCCTAAGGACACCCTGATGATCTCTCGGACCC CTGAAGTGACCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCGAAGTGAA GTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCT AGAGAGGAACAGTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGC TGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAA GGCCCTGCCTGCTCCTATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCT AGGGAACCCCAGGTTTACACCCTGCCTCCATGCCGGGAAGAGATGACCAAGA ACCAGGTGTCCCTGTGGTGCCTGGTTAAGGGCTTCTACCCCTCCGATATCGC

		CGTGGAATGGGAGTCTAATGGCCAGCCTGAGAACAACTACAAGACAACCCCT CCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACTCCAAGCTGACAGTGG ACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGA GGCCCTGCACAATCACTACACCCAGAAGTCCCTGTCTCTGTCTCCCGGAAAA GGCGGCGGAGGATCTGGCGGAGGTGGTAGCGGAGGCGGTGGATCTGAAGTTC AGCTGGTTGAGAGTGGCGGCGGACTGGTTAAGCCTGGTGGTTCTCTGAGACT GAGCTGCGCCGCTTCTGGCTTCACATTCAGCCCCTACTCCGTGTTCTGGGTT CGACAAGCTCCAGGCAAGGGCCTCGAATGGGTGTCCTCTATCAACACCGACA GCACCTACAAGTATTACGCTGACAGCGTGAAAGGCCGGTTTACCATCAGCAG AGACAACGCCGAGAACTCCATCTTCCTCCAGATGAATTCTCTGCGCGCTGAG GATACCGCTGTGTACTACTGCGCCAGAGACAGATCCTACTACGCCTTCTCCT CCGGCTCTCTGTCTGACTACTACTACGGCCTGGATGTGTGGGGCCAGGGAAC ACTTGTGACAGTGTCAAGTGGCGGTGGCGGTAGTGGCGGAGGCGGTTCTGGT GGTGGTGGTTCAGGCGGTGGTGGCAGCGATATCGTGATGACCCAGTCTCCAC TGAGCCTGAGCGTGACACCTGGCGAGCCTGCCTCTATCTCCTGCAGATCCTC TCAGTCCCTGCTGCACACCAACCTGTACAACTACCTGGATTGGTATGTGCAG AAGCCCGGCCAGTCTCCTCAGCTGCTGATCTACCTGGCCTCCAACAGAGCTT CTGGCGTGCCCGATAGATTCTCCGGTTCTGGCTCTGGCACCGACTTCACCCT GAAGATTTCCAGAGTGGAAACAGAGGACGTGGGCGTGTACTATTGCATGCAG GCTCTGCAGATTCCCCGGACCTTCGGCCAGGGCACCAAACTGGAAATCAAGT GATGA
SEQ ID NO: 80	α-CTLA4 light - hCLIg_vk - IL2	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGGCACACTGTCACTGTCTCC AGGCGAGAGAGCTACCCTGTCCTGTAGAGCCTCTCAGTCCGTGGGCTCCTCT TACCTGGCTTGGTATCAGCAGAAGCCCGGCCAGGCTCCTAGACTGTTGATCT ACGGCGCCTTCTCCAGAGCCACAGGCATCCCTGATAGATTCTCCGGCTCTGG CTCTGGCACCGACTTCACCCTGACCATCTCCAGACTGGAACCCGAGGACTTC GCCGTGTACTACTGTCAGCAGTACGGCTCCTCTCCTTGGACCTTTGGCCAGG GCACCAAGGTGGAAATCAAGCGGACAGTGGCCGCTCCTTCCGTGTTCATCTT CCCACCTTCCGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTG CTGAACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATG CCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGA CAGCACCTACAGCCTGTCCTCCACACTGACCCTGTCCAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGCGAAGTGACCCATCAGGGCCTGTCTAGCCCTG TGACCAAGTCTTTCAACAGAGGCGAGTGTGGCGGCGGAGGATCTGGCGGAGG TGGAAGCGGAGGCGGTGGATCTGCTCCTACCTCCTCCAGCACCAAGAAAACC CAGCTGCAGTTGGAGCATCTGCTGCTGGACCTGCAGATGATCCTGAACGGCA TCAACAACTACAAGAACCCCAAGCTGACCCGGATGCTGACCGCCAAGTTTGC CATGCCTAAGAAGGCCACCGAGCTGAAACATCTGCAGTGCCTGGAAGAGGAA CTGAAGCCCCTGGAAGAAGTGCTGAATCTGGCCCAGTCCAAGAACTTCCACC TGAGGCCTCGGGACCTGATCTCCAACATCAACGTGATCGTGCTCGAGCTGAA GGGCTCCGAGACAACCTTCATGTGCGAGTACGCCGACGAGACTGCTACCATC GTGGAATTTCTGAACCGGTGGATCACCTTCTGCCAGTCCATCATCTCTACCC TGACCTGATGA
SEQ ID NO: 81	α-TRAILR2 heavy - hCHIg_Hole_Cys	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGCGAAGTGCAGCTGGTTCAATCTGGCGGCGGAGTGGAAAGACCTGG CGGATCTCTGAGACTGTCTTGTGCCGCCTCTGGCTTCACCTTCGACGACTAC GGAATGTCCTGGGTCCGACAGGCTCCTGGCAAAGGACTGGAATGGGTGTCCG GCATCAATTGGAACGGCGGCTCTACCGGCTACGCCGACTCTGTGAAGGGCAG AGTGACCATCTCCAGAGACAACGCCAAGAACTCCCTGTACCTGCAGATGAAC AGCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTGCTAAGATCCTCGGCG

		CTGGCAGAGGCTGGTACTTTGATCTGTGGGGCAAGGGCACCACCGTGACCGT TTCTTCCGCTTCCACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTCCAGC AAGTCTACCTCTGGCGGAACAGCTGCTCTGGGCTGCCTGGTCAAGGACTACT TTCCTGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTGACATCTGGCGT GCACACCTTTCCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCT GTCGTGACCGTGCCTTCCAGCTCTCTGGGAACCCAGACCTACATCTGCAATG TGAACCACAAGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAAGTC CTGCGACAAGACCCACACCTGTCCTCCATGTCCTGCTCCAGAACTGCTCGGC GGACCTTCCGTGTTCCTGTTTCCTCCAAAGCCTAAGGACACCCTGATGATCT CTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTCACGAGGATCC CGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAATGCCAAG ACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACAGAGTGGTGTCCGTGC TGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGT GTCCAACAAGGCCCTGCCTGCTCCTATCGAAAAGACCATCAGCAAGGCCAAG GGCCAGCCTCGGGAACCTCAAGTCTGTACCCTGCCTCCTAGCCGGGAAGAGA TGACCAAGAACCAGGTGTCCCTGTCCTGTGCCGTGAAGGGCTTCTACCCTTC CGATATCGCCGTGGAATGGGAGAGCAATGGCCAGCCAGAGAACAACTACAAG ACAACCCCTCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGGTGTCCAAGC TGACAGTGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGT GATGCACGAGGCCCTGCACAATCACTACACCCAGAAGTCCCTGTCTCTGAGC CCCGGCAAGTGATGA
SEQ ID NO: 82	α-meso AB237 heavy - hCHIg_Knob_Cys	ATGGAAACCGATACACTGCTGCTGTGGGTGCTGCTCCTCTGGGTGCCAGGAT CTACAGGCCAGGTCCAGCTGCAGGAAAGCGGCCCTGGACTGGTCAAGCCTAG CCAGACCCTGAGCCTGACCTGTACCGTGTCCGGCGGCAGCATCAACAACAAC AATTACTACTGGACATGGATCCGGCAGCACCCCGGCAAGGGCCTGGAATGGA TCGGCTACATCTACTACAGCGGCTCCACCTTCTACAACCCCAGCCTGAAGTC CAGAGTGACCATCAGCGTGGACACCAGCAAGACCCAGTTCTCCCTGAAGCTG AGCAGCGTGACAGCCGCCGACACAGCCGTGTACTACTGCGCCAGAGAAGATA CCATGACCGGCCTGGATGTGTGGGGCCAGGGCACCACAGTGACAGTGTCTAG CGCCAGCACCAAGGGCCCTAGCGTGTTCCCTCTGGCCCCTAGCTCTAAGAGC ACATCTGGCGGAACAGCCGCCCTGGGCTGCCTGGTCAAGGATTACTTTCCTG AGCCCGTGACCGTGTCCTGGAACTCTGGTGCTCTGACCAGCGGCGTGCACAC CTTTCCAGCTGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCTAGCGTGGTC ACAGTGCCTAGCAGCAGCCTGGGCACACAGACCTACATCTGCAACGTGAACC ACAAGCCCAGCAACACCAAGGTGGACAAGCGGGTGGAACCCAAGAGCTGCGA CAAGACCCACACCTGTCCTCCCTGTCCTGCCCCTGAACTGCTGGGCGGACCT TCCGTGTTCCTGTTCCCTCCAAAGCCCAAGGACACCCTGATGATCAGCCGGA CCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGATCCCGAAGT GAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAG CCCAGAGAGGAACAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCG TGCTGCACCAGGACTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAA CAAGGCCCTGCCAGCCCCTATCGAGAAAACCATCAGCAAGGCCAAGGGCCAG CCCCGCGAACCTCAGGTGTACACACTGCCTCCCTGCCGGGAAGAGATGACCA AGAACCAGGTGTCCCTGTGGTGTCTCGTGAAGGGCTTCTACCCCTCCGATAT CGCCGTGGAATGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACC CCTCCCGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACTCCAAACTGACCG TGGACAAGAGCCGGTGGCAGCAGGGCAATGTGTTCAGCTGTAGCGTGATGCA CGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCTGGC AAGTAATGA
SEQ ID	α-meso AB237 light	ATGGAAACCGATACACTGCTGCTGTGGGTGCTGCTCCTCTGGGTGCCAGGCA GCACCGGCGATATCCAGATGACACAGAGCCCTAGCAGCCTGAGCGCCAGCGT

NO: 83	- hCLIg_vk	GGGCGATAGAGTGACCATCACCTGTCGGGCCAGCCAGAGCATCAACAACTAC CTGAACTGGTATCAGCAGAAGCCCGGCAAGGCCCCTACCCTGCTGATCTATG CCGCTTCTAGCCTGCAGAGCGGCGTGCCCAGCAGATTTTCTGGCAGCAGATC CGGCACCGACTTCACCCTGACAATCAGCAGCCTGCAGCCCGAGGACTTCGCC GCCTACTTCTGCCAGCAGACCTACAGCAATCCCACCTTCGGCCAGGGCACCA AGGTGGAAGTGAAGAGAACAGTGGCCGCTCCCAGCGTGTTCATCTTCCCACC CAGCGACGAGCAGCTGAAGTCTGGCACAGCCAGCGTCGTGTGCCTGCTGAAC AACTTCTACCCCAGAGAAGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGC AGTCCGGCAACAGCCAGGAAAGCGTCACCGAGCAGGACAGCAAGGACTCCAC CTACAGCCTGTCCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCAC AAAGTGTACGCCTGCGAAGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCA AGAGCTTCAATAGAGGCGAGTGCTAATGA
SEQ ID NO: 84	α-PDL1 heavy - hCHIg_Hole_Cys	ATGGAAACCGATACCCTGCTGCTGTGGGTGCTGCTCCTCTGGGTGCCAGGAT CTACAGGCGAGGTGCAGCTGCTGGAATCTGGCGGAGGACTGGTGCAGCCTGG CGGCTCTCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCAGCTAT ATCATGATGTGGGTCCGACAGGCCCCTGGCAAGGGCCTGGAATGGGTGTCCT CTATCTACCCCTCCGGCGGCATCACCTTTTACGCCGACACCGTGAAGGGCCG GTTCACCATCTCCCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGCGCTAGAATCAAGCTGG GCACCGTGACCACCGTGGACTATTGGGGCCAGGGCACCCTGGTCACCGTGTC CTCTGCTTCTACCAAGGGCCCCTCCGTGTTCCCTCTGGCCCCTTCCAGCAAG TCCACCTCTGGCGGAACCGCTGCTCTGGGCTGCCTGGTCAAGGACTACTTCC CCGAGCCCGTGACCGTGTCTTGGAACTCTGGCGCCCTGACCAGCGGCGTGCA CACATTTCCAGCCGTGCTGCAGTCCAGCGGCCTGTACTCTCTGTCCTCCGTC GTGACAGTGCCCTCCAGCTCTCTGGGCACACAGACCTACATCTGCAACGTGA ACCACAAGCCCTCCAACACCAAGGTGGACAAGCGGGTGGAACCCAAGTCCTG CGACAAGACCCACACCTGTCCTCCCTGTCCTGCCCCTGAACTGCTGGGCGGA CCCAGCGTGTTCCTGTTCCCTCCAAAGCCTAAGGACACCCTGATGATCTCCC GGACCCCTGAAGTGACCTGCGTGGTGGTGGACGTGTCCCACGAGGATCCCGA AGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACC AAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTGGTGTCCGTGCTGA CAGTGCTGCATCAGGACTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTC CAACAAGGCCCTGCCAGCCCCTATCGAAAAGACCATCTCCAAGGCCAAGGGC CAGCCAAGAGAGCCTCAAGTCTGCACACTGCCTCCCAGCCGGGAAGAGATGA CCAAGAACCAGGTGTCCCTGAGCTGCGCTGTGAAGGGCTTCTACCCTTCCGA TATCGCCGTGGAATGGGAGAGCAACGGCCAGCCCGAGAACAATTACAAGACC ACCCCTCCCGTGCTGGACTCCGACGGCTCATTCTTCCTGGTGTCCAAGCTGA CCGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCTGTGAT GCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGTCTCCC GGCAAGTAATGA
SEQ ID NO: 85	α-PDL1 light - hCLIg_vl	ATGGAAACCGATACCCTGCTGCTGTGGGTGCTGCTCCTCTGGGTGCCAGGCT CTACCGGCCAGTCTGCTCTGACCCAGCCTGCCTCTGTGTCTGGCTCCCCTGG CCAGTCCATCACCATCAGCTGTACCGGCACCTCCTCCGACGTGGGCGGCTAC AACTACGTGTCCTGGTATCAGCAGCATCCCGGCAAGGCCCCTAAGCTGATGA TCTACGACGTGTCCAACCGGCCCTCCGGCGTGTCCAATCGGTTCTCTGGCTC CAAGTCCGGCAACACCGCCTCCCTGACAATCAGCGGACTGCAGGCCGAGGAC GAGGCCGACTACTACTGCTCCTCCTACACCTCCAGCTCTACCCGGGTGTTCG GCACCGGCACCAAAGTGACAGTGCTGGGCCAGCCCAAGGCCAACCCCACCGT GACCCTGTTCCCTCCATCCTCCGAGGAACTGCAGGCTAACAAGGCCACCCTC GTGTGCCTGATCTCCGACTTCTACCCTGGCGCCGTGACCGTGGCTTGGAAGG CTGATGGCTCTCCTGTGAAGGCCGGCGTGGAAACCACCAAGCCCTCCAAGCA

		GTCCAACAACAAATACGCCGCCTCCAGCTACCTGTCCCTGACCCCTGAGCAG TGGAAGTCCCACCGGTCCTACAGCTGCCAGGTCACACATGAGGGCTCCACCG TGGAAAAGACCGTGGCCCCTACCGAGTGCTCCTAATGA
SEQ ID NO: 86	α-HER3 heavy - mFc_Knob_ Cys	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGCTGGTTCAGTCTGGCGGAGGATTGGTTCAGCCAGG CGGATCCCTGAGACTGTCTTGTGCCGCTTCTGGCTTCACCTTCGACGACTAC GCTATGCACTGGGTCCGACAGGCCCCTGGCAAAGGATTGGAATGGGTGGCCG GCATCTCTTGGGACTCTGGCTCTACCGGCTACGCCGACTCTGTGAAGGGCAG ATTCACCATCTCTCGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAAC AGCCTGAGAGCCGAGGACACCGCTCTGTACTACTGCGCTAGAGATCTGGGCG CCTACCAGTGGGTGGAAGGCTTTGATTATTGGGGCCAGGGCACCCTGGTCAC CGTGTCCTCTGCTTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTCC AGCAAGTCTACCTCTGGCGGAACAGCTGCTCTGGGCTGCCTGGTCAAGGACT ACTTTCCTGAGCCTGTGACCGTGTCTTGGAACTCCGGCGCTCTGACATCTGG CGTGCACACCTTTCCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCC TCTGTCGTGACCGTGCCTTCCAGCTCTCTGGGAACCCAGACCTACATCTGCA ATGTGAACCACAAGCCTAGCAACACCAAGGTGGACAAGAGAGTGGAACCCAA GTCCTGCACCATCAAGCCCTGTCCTCCATGCAAGTGCCCCGCTCCTAATCTG CTCGGAGGCCCTTCCGTGTTCATCTTCCCACCTAAGATCAAGGACGTGCTGA TGATCTCCCTGTCTCCTATCGTGACCTGCGTGGTGGTGGACGTGTCCGAGGA TGATCCTGACGTGCAGATCAGTTGGTTCGTGAACAACGTGGAAGTGCACACC GCTCAGACCCAGACACACAGAGAGGACTACAACAGCACCCTGAGAGTGGTGT CTGCCCTGCCTATCCAGCACCAGGATTGGATGTCCGGCAAAGAATTCAAGTG CAAAGTCAACAACAAGGACCTGCCTGCTCCAATCGAGCGGACCATCTCTAAG CCTAAGGGCTCTGTCAGGGCCCCTCAGGTGTACGTTCTGCCTCCTTGCGAGG AAGAGATGACCAAGAAACAAGTGACCCTGTGGTGCATGGTCACCGACTTCAT GCCCGAGGACATCTACGTGGAATGGACCAACAACGGCAAGACCGAGCTGAAC TACAAGAACACCGAGCCTGTGCTGGACTCCGACGGCTCCTACTTCATGTACT CCAAGCTGCGCGTCGAGAAGAAGAACTGGGTCGAGAGAAACTCCTACTCCTG CTCCGTGGTGCACGAGGGCCTGCACAATCACCACACCACCAAGTCCTTCTCT CGGACCCCTGGAAAGTGATGA
SEQ ID NO: 87	α-IGF1R heavy - mFc_Hole_ Cys	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGCGAAGTGCAGCTGTTGCAGTCTGGCGGAGGATTGGTTCAGCCTGG CGGATCCCTGAGACTGTCTTGTGCCGCCTCTGGCTTCATGTTCAGCAGATAC CCCATGCACTGGGTCCGACAGGCCCCTGGAAAAGGACTGGAATGGGTCGGAT CCATCTCCGGAAGTGGCGGCGCTACCCCTTACGCCGATTCTGTGAAGGGCAG ATTCACCATCAGCCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGAGAGCCGAGGACACCGCCGTGTACTACTGCGCCAAGGACTTCTACC AGATCCTGACCGGCAACGCCTTCGACTATTGGGGCCAGGGCACAACCGTGAC CGTGTCCTCTGCTTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTCC AGCAAGTCTACCTCTGGCGGAACAGCTGCTCTGGGCTGCCTGGTCAAGGACT ACTTTCCTGAGCCTGTGACAGTGTCCTGGAACTCTGGCGCTCTGACATCCGG CGTGCACACCTTTCCAGCTGTGCTGCAATCCAGCGGCCTGTACTCTCTGTCC TCCGTCGTGACAGTGCCTTCCAGCTCTCTGGGAACCCAGACCTACATCTGCA ATGTGAACCACAAGCCTTCCAACACCAAGGTGGACAAGAGAGTGGAACCCAA GTCCTGCACCATCAAGCCCTGTCCTCCATGCAAGTGCCCCGCTCCTAATCTG CTCGGAGGCCCTTCCGTGTTCATCTTCCCACCTAAGATCAAGGACGTGCTGA TGATCTCCCTGTCTCCTATCGTGACCTGCGTGGTGGTGGACGTGTCCGAGGA TGATCCTGACGTGCAGATCAGTTGGTTCGTGAACAACGTGGAAGTGCACACC GCTCAGACCCAGACACACAGAGAGGACTACAACAGCACCCTGAGAGTGGTGT CTGCCCTGCCTATCCAGCACCAGGATTGGATGTCCGGCAAAGAATTCAAGTG

		CAAAGTCAACAACAAGGACCTGCCTGCTCCAATCGAGCGGACCATCTCTAAG CCTAAGGGCTCTGTGCGGGCTCCCCAAGTTTGTGTTCTGCCTCCACCTGAGG AAGAGATGACCAAGAAACAAGTGACCCTGTCCTGCGCCGTGACCGACTTCAT GCCTGAGGACATCTACGTGGAATGGACCAACAACGGCAAGACCGAGCTGAAT TACAAGAACACAGAGCCTGTGCTGGACTCCGACGGCTCCTACTTCATGGTGT CTAAGCTGCGCGTCGAGAAGAAGAACTGGGTCGAGAGAAACTCCTACTCCTG CTCCGTGGTGCACGAGGGCCTGCACAATCACCACACCACCAAGTCCTTCTCT CGGACCCCTGGCAAGTGATGA
SEQ ID NO: 88	α-CD221 heavy - hCHIg_Hole_Cys	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGCGAAGTGCAGCTGGTTCAGTCTGGCGCCGAAGTGAAGAAACCTGG CTCCTCCGTGAAGGTGTCCTGCAAGGCTTCTGGCGGCACCTTCTCCTCTTAC GCCATCTCCTGGGTCCGACAGGCTCCTGGACAAGGCTTGGAATGGATGGGCG GCATCATCCCCATCTTCGGCACCGCCAATTACGCCCAGAAATTCCAGGGCAG AGTGACCATCACCGCCGACAAGTCTACCTCCACCGCCTACATGGAACTGTCC AGCCTGAGATCTGAGGACACCGCCGTGTACTACTGCGCTAGAGCCCCTCTGA GATTCCTGGAATGGTCTACCCAGGACCACTACTACTATTACTACATGGACGT GTGGGGCAAGGGCACCACCGTGACAGTTTCTTCCGCCTCCACCAAGGGACCC AGCGTTTTCCCTCTGGCTCCATCCTCCAAGTCCACCTCTGGTGGAACAGCTG CTCTGGGCTGCCTGGTCAAGGACTACTTTCCTGAGCCTGTGACCGTGTCCTG GAACTCTGGCGCTCTGACATCTGGCGTGCACACCTTTCCAGCTGTGCTGCAG TCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCTTCCAGCTCTC TGGGAACCCAGACCTACATCTGCAATGTGAACCACAAGCCTTCCAACACCAA GGTCGACAAGAGAGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCT CCATGTCCTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCCTGTTTCCTC CAAAGCCTAAGGACACCCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGT GGTGGTGGATGTGTCTCACGAGGACCCAGAAGTGAAGTTCAATTGGTACGTG GACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACA ACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCT GAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCTCCT ATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGGGAACCTCAAGTCT GTACCCTGCCTCCTAGCCGGGAAGAGATGACCAAGAACCAGGTGTCCCTGTC CTGTGCCGTGAAGGGCTTCTACCCTTCCGATATCGCCGTGGAATGGGAGAGC AATGGCCAGCCAGAGAACAACTACAAGACAACCCCTCCTGTGCTGGACTCCG ACGGCTCATTCTTCCTGGTGTCCAAGCTGACAGTGGACAAGTCCAGATGGCA GCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAATCAC TACACACAGAAGTCCCTGTCTCTGAGCCCCGGCAAGTGATGA
SEQ ID NO: 89	α-PD1 heavy - hCHIg_Knob_Cys	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGCTGGTGGAATCTGGTGGCGGAGTTGTGCAGCCTGG CAGATCTCTGAGACTGGACTGCAAGGCCTCCGGCATCACCTTCTCCAACTCT GGCATGCACTGGGTCCGACAGGCCCCTGGAAAAGGACTGGAATGGGTCGCCG TGATTTGGTACGACGGCTCCAAGAGGTACTACGCCGACTCCGTGAAGGGCAG ATTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTTTCTGCAGATGAAC TCCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTGCCACCAACGACGATT ATTGGGGCCAGGGCACACTGGTCACCGTGTCCTCTGCTTCTACCAAGGGACC CAGCGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACCTCTGGCGGAACAGCT GCTCTGGGCTGCCTGGTCAAGGACTACTTTCCTGAGCCTGTGACCGTGTCTT GGAACTCTGGCGCTCTGACATCCGGCGTGCACACCTTTCCAGCTGTGCTGCA ATCCTCCGGCCTGTACTCTCTGTCCTCCGTCGTGACCGTGCCTTCTAGCTCT CTGGGCACCCAGACCTACATCTGCAATGTGAACCACAAGCCTTCCAACACCA AGGTGGACAAGAGAGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCC ACCATGTCCTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCCTGTTTCCT

		CCAAAGCCTAAGGACACCCTGATGATCTCTCGGACCCCTGAAGTGACCTGCG TGGTGGTGGATGTGTCTCACGAGGATCCCGAAGTGAAGTTCAATTGGTACGT GGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTAC AACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGC TGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCTCC TATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTAGGGAACCCCAGGTT TACACCCTGCCTCCATGCCGGGAAGAGATGACCAAGAACCAGGTGTCCCTGT GGTGCCTGGTTAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTC TAATGGCCAGCCTGAGAACAACTACAAGACAACCCCTCCTGTGCTGGACTCC GACGGCTCATTCTTCCTGTACTCCAAGCTGACAGTGGACAAGTCCAGATGGC AGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAATCA CTACACCCAGAAGTCCCTGTCTCTGTCCCCTGGCAAGTGATGA
SEQ ID NO: 90	α-PD1 light - hCLIg_vk	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGCGAGATCGTGCTGACCCAGTCTCCTGCCACACTGTCACTGTCTCC AGGCGAGAGAGCTACCCTGTCCTGTAGAGCCTCTCAGTCCGTGTCCTCTTAC CTGGCCTGGTATCAGCAGAAGCCTGGACAGGCTCCCCGGCTGCTGATCTACG ATGCCTCTAATAGAGCCACAGGCATCCCCGCCAGATTCTCCGGATCTGGCTC TGGCACAGACTTTACCCTGACCATCTCCAGCCTGGAACCTGAGGACTTCGCC GTGTACTACTGCCAGCAGTCCTCTAACTGGCCTCGGACCTTTGGCCAGGGCA CCAAGGTGGAAATCAAGCGGACAGTGGCCGCTCCTTCCGTGTTCATCTTCCC ACCTTCCGACGAGCAGCTGAAGTCTGGCACCGCTTCTGTCGTGTGCCTGCTG AACAACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCC TGCAGTCCGGCAACTCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACAG CACCTACAGCCTGTCCTCCACACTGACCCTGTCCAAGGCCGACTACGAGAAG CACAAGGTGTACGCCTGCGAAGTGACCCATCAGGGCCTGTCTAGCCCTGTGA CCAAGTCTTTCAACCGGGGCGAGTGCTGATGA
SEQ ID NO: 91	α-IL12β heavy - hCHIg_Hole_Cys	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTCTTGTGGGTGCCAGGAT CTACAGGACAGGTGCAGCTGGTGGAATCTGGTGGCGGAGTTGTGCAGCCTGG CAGATCCCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCTCTTAC GGAATGCACTGGGTCCGACAGGCCCCTGGCAAAGGATTGGAGTGGGTCGCCT TCATCAGATACGACGGCTCCAACAAGTACTACGCCGACTCCGTGAAGGGCAG ATTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGAAC TCCCTGAGAGCCGAGGACACCGCCGTGTACTACTGCAAGACCCACGGCTCTC ACGACAATTGGGGCCAGGGCACAATGGTCACCGTGTCCTCTGCTTCCACCAA GGGACCCTCTGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACCTCTGGCGGA ACAGCTGCTCTGGGCTGCCTGGTCAAGGACTACTTTCCTGAGCCTGTGACCG TGTCTTGGAACTCTGGCGCTCTGACATCCGGCGTGCACACCTTTCCAGCTGT GCTGCAATCCTCCGGCCTGTACTCTCTGTCCTCCGTCGTGACCGTGCCTTCT AGCTCTCTGGGCACCCAGACCTACATCTGCAATGTGAACCACAAGCCTTCCA ACACCAAGGTGGACAAGAGAGTGGAACCCAAGTCCTGCGATAAGACCCACAC CTGTCCACCATGTCCTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCCTG TTTCCTCCAAAGCCTAAGGACACCCTGATGATCTCTCGGACCCCTGAAGTGA CCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCGAAGTGAAGTTCAATTG GTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAA CAGTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGG ATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCC TGCTCCTATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGGGAACCT CAAGTCTGTACCCTGCCTCCTAGCCGGGAAGAGATGACCAAGAACCAGGTGT CCCTGTCCTGCGCTGTGAAGGGCTTCTACCCTTCCGATATCGCCGTGGAATG GGAGAGCAATGGCCAGCCTGAGAACAACTACAAGACCACACCTCCTGTGCTG GACTCCGACGGCTCATTCTTCCTGGTGTCCAAGCTGACAGTGGACAAGTCCA

		GATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCA CAATCACTACACCCAGAAGTCCCTGTCTCTGAGCCCCGGCAAGTGATGA

2. Expression and purification of NanoBiT constructs.

The plasmids were co-transfected into ExpiCHO cells (Life Technologies A29127). Transfections were performed using 1 mg of total DNA per liter for a multispecific construct with a 1:1:1 heavy chain to light chain to competing light chain ratio. The ExpiCHO transfection was performed according to the manufacturer's instructions. ExpiCHO cells were grown for 7 days at 32 °C with 5 % CO_2 after transfection. The cells were pelleted by centrifugation at 3000 x g. CaptureSelect CH1-XL affinity resin (GE 2943452010) was added to the supernatant and incubated for 1-3 hours at room temperature. The resin was packed into a fritted filter plate (Nunc fritted deepwell filter plates 278011), washed with 3 x 1 mL of Dulbecco's phosphate-buffered saline (DPBS, Life Technologies 14190-144). The bound protein was eluted from the column with 20 mM citrate, 100 mM NaCl, pH 2.9. The elution fractions were neutralized using 1 M Tris-HCl, pH 8.0. Table 2 shows the amino acid sequences for all the NanoBiT constructs.

Table 2. Amino Acid sequences for NanoBiT constructs. All constructs contained an Ig Kappa leader sequence (SEQ ID NO 214: METDTLLLWVLLLWVPGSTG).

SEQ ID NO	Amino Acid Sequence	Description	Germline	Corresponding DNA SEQ ID NO
SEQ ID NO: 92	QVQLVESGGGVVQPGRSLRLSCAASGFAFSSYGM HWVRQAPGKGLEWVAVIWFDGTKKYYTDSVKGRF TISRDNSKNTLYLQMNTLRAEDTAVYYCARDRGI GARRGPYYMDVWGKGTTVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKRVEPKSCGSSGGGGSGGG GSSGGVFTLEDFVGDWEQTAAYNLDQVLEQGGVS SLLQNLAVSVTPIQRIVRSGENALKIDIHVIIPY EGLSADQMAQIEEVFKVVYPVDDHHFKVILPYGT LVIDGVTPNMLNYFGRPYEGIAVFDGKKITVTGT LWNGNKIIDERLITPDGSMLFRVTINS	α-amyloid β heavy - LgBiT	VH3-33*01 (SEQ ID NO: 193)	SEQ ID NO: 1
SEQ ID NO: 93	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGECGSSGGGGSGGGGSSGGVTGYRLFE EIL	α-amyloid β light - SmBiT	Vk1-39*01 (SEQ ID NO: 201)	SEQ ID NO: 2

SEQ ID NO: 94	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	α-amyloid β light	Vk1-39*01 (SEQ ID NO: 201)	SEQ ID NO: 3
SEQ ID NO: 95	EVQLVQSGAEVKKSGESLKISCKGSGYSFTSYWI GWVRQMPGKGLEWMGIFYPGDSSTRYSPSFQGQV TISADKSVNTAYLQWSSLKASDTAMYYCARRRNW GNAFDIWGQGTMVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKRVEPKSCGSSGGGGSGGGGSSGG VFTLEDFVGDWEQTAAYNLDQVLEQGGVSSLLQN LAVSVTPIQRIVRSGENALKIDIHVIIPYEGLSA DQMAQIEEVFKVVYPVDDHHFKVILPYGTLVIDG VTPNMLNYFGRPYEGIAVFDGKKITVTGTLWNGN KIIDERLITPDGSMLFRVTINS	α-Clostridium difficile toxin B heavy - LgBiT	VH5-51*01 (SEQ ID NO: 198)	SEQ ID NO: 4
SEQ ID NO: 96	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYL AWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYCQQYGSSTWTFGQG TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGECGSSGGGGSGGGGSSGGVTGYRLF EEIL	α-Clostridium difficile toxin B light - SmBiT	Vk3-20*01 (SEQ ID NO: 205)	SEQ ID NO: 5
SEQ ID NO: 97	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYL AWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYCQQYGSSTWTFGQG TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC	α-Clostridium difficile toxin B light	Vk3-20*01 (SEQ ID NO: 205)	SEQ ID NO: 6
SEQ ID NO: 98	EGQLVQSGGGLVHPGGSLRLSCAGSGFTFSSYGM HWVRQAPGKGLEWVSGIGTGGGTYSTDSVKGRFT ISRDNAKNSLYLQMNSLRAEDMAVYYCARGDYYG SGSFFDCWGQGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKRVEPKSCGSSGGGGSGGGGSSG GVFTLEDFVGDWEQTAAYNLDQVLEQGGVSSLLQ NLAVSVTPIQRIVRSGENALKIDIHVIIPYEGLS ADQMAQIEEVFKVVYPVDDHHFKVILPYGTLVID GVTPNMLNYFGRPYEGIAVFDGKKITVTGTLWNG NKIIDERLITPDGSMLFRVTINS	α-connective tissue growth factor heavy - LgBiT	VH3-13*01 (SEQ ID NO: 188)	SEQ ID NO: 7
SEQ ID NO: 99	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLA WYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQYNSYPPTFGQGT KLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD	α-connective tissue growth factor light	Vk1D-16*01 (SEQ ID NO: 202)	SEQ ID NO: 8

	STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGECGSSGGGGSGGGGSSGGVTGYRLFE EIL	- SmBiT		
SEQ ID NO: 100	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLA WYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQYNSYPPTFGQGT KLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	α-connective tissue growth factor light	Vk1D-16*01 (SEQ ID NO: 202)	SEQ ID NO: 9
SEQ ID NO: 101	QVQLVQSGAEVKKPGASVKVSCKASGYSFTNYYI HWVRQAPGQRLEWMGWINAGNGNTKYSQKFQGRV TITRDTSASTAYMELSSLRSEDTAVYYCVRRQRF PYYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKRVEPKSCGSSGGGGSGGGGSSGG VFTLEDFVGDWEQTAAYNLDQVLEQGGVSSLLQN LAVSVTPIQRIVRSGENALKIDIHVIIPYEGLSA DQMAQIEEVFKVVYPVDDHHFKVILPYGTLVIDG VTPNMLNYFGRPYEGIAVFDGKKITVTGTLWNGN KIIDERLITPDGSMLFRVTINS	α-CSF2 heavy - LgBiT	VH1-3*01 (SEQ ID NO: 185)	SEQ ID NO: 10
SEQ ID NO: 102	EIVLTQSPATLSVSPGERATLSCRASQSVGTNVA WYQQKPGQAPRVLIYSTSSRATGITDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQFNKSPLTFGGGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGECGSSGGGGSGGGGSSGGVTGYRLFE EIL	α-CSF2 light - SmBiT	Vk3D-20*01 (SEQ ID NO: 206)	SEQ ID NO: 11
SEQ ID NO: 103	EIVLTQSPATLSVSPGERATLSCRASQSVGTNVA WYQQKPGQAPRVLIYSTSSRATGITDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQFNKSPLTFGGGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	α-CSF2 light	Vk3D-20*01 (SEQ ID NO: 206)	SEQ ID NO: 12
SEQ ID NO: 104	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTM HWVRQAPGKGLEWVTFISYDGNNKYYADSVKGRF TISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWL GPFDYWGQGTLVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCGSSGGGGSGGGGSSGGV FTLEDFVGDWEQTAAYNLDQVLEQGGVSSLLQNL AVSVTPIQRIVRSGENALKIDIHVIIPYEGLSAD QMAQIEEVFKVVYPVDDHHFKVILPYGTLVIDGV TPNMLNYFGRPYEGIAVFDGKKITVTGTLWNGNK IIDERLITPDGSMLFRVTINS	α-CTLA4 heavy - LgBiT	VH3-30*01 (SEQ ID NO: 192)	SEQ ID NO: 13
SEQ ID NO:	EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYL AWYQQKPGQAPRLLIYGAFSRATGIPDRFSGSGS	α-CTLA4 light	Vk3-20*01	SEQ ID NO: 14

105	GTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQG TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGECGSSGGGGSGGGGSSGGVTGYRLF EEIL	SmBiT	(SEQ ID NO: 205)	
SEQ ID NO: 106	EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYL AWYQQKPGQAPRLLIYGAFSRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQG TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC	α-CTLA4 light	Vk3-20*01 (SEQ ID NO: 205)	SEQ ID NO: 15
SEQ ID NO: 107	EVQLVQSGAEVKKPGESLKISCKGSGYIFTNYWI AWVRQMPGKGLESMGIIYPGDSDIRYSPSFQGQV TISADKSITTAYLQWSSLKASDTAMYYCARHDIE GFDYWGRGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKRVEPKSCGSSGGGGSGGGGSSGGVF TLEDFVGDWEQTAAYNLDQVLEQGGVSSLLQNLA VSVTPIQRIVRSGENALKIDIHVIIPYEGLSADQ MAQIEEVFKVVYPVDDHHFKVILPYGTLVIDGVT PNMLNYFGRPYEGIAVFDGKKITVTGTLWNGNKI IDERLITPDGSMLFRVTINS	α-IFN heavy - LgBiT	VH5-51*01 (SEQ ID NO: 198)	SEQ ID NO: 16
SEQ ID NO: 108	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSFF AWYQQKPGQAPRLLIYGASSRATGIPDRLSGSGS GTDFTLTITRLEPEDFAVYYCQQYDSSAITFGQG TRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGECGSSGGGGSGGGGSSGGVTGYRLF EEIL	α-IFN light - SmBiT	Vk3-20*01 (SEQ ID NO: 205)	SEQ ID NO: 17
SEQ ID NO: 109	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSFF AWYQQKPGQAPRLLIYGASSRATGIPDRLSGSGS GTDFTLTITRLEPEDFAVYYCQQYDSSAITFGQG TRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC	α-IFN light	Vk3-20*01 (SEQ ID NO: 205)	SEQ ID NO: 18
SEQ ID NO: 110	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYSI SWVRQAPGQGLEWMGWISVYNGNTNYAQKFQGRV TMTTDTSTSTAYLELRSLRSDDTAVYYCARDPIA AGYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKRVEPKSCGSSGGGGSGGGGSSGGVFT LEDFVGDWEQTAAYNLDQVLEQGGVSSLLQNLAV SVTPIQRIVRSGENALKIDIHVIIPYEGLSADQM AQIEEVFKVVYPVDDHHFKVILPYGTLVIDGVTP NMLNYFGRPYEGIAVFDGKKITVTGTLWNGNKII	α-IFNα heavy - LgBiT	VH1-18*01 (SEQ ID NO: 183)	SEQ ID NO: 19

	DERLITPDGSMLFRVTINS			
SEQ ID NO: 111	EIVLTQSPGTLSLSPGERATLSCRASQSVSSTYL AWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYCQQYGSSPRTFGQG TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGECGSSGGGGSGGGGSSGGVTGYRLF EEIL	α-IFNα light - SmBiT	Vk3-20*01 (SEQ ID NO: 205)	SEQ ID NO: 20
SEQ ID NO: 112	EIVLTQSPGTLSLSPGERATLSCRASQSVSSTYL AWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYCQQYGSSPRTFGQG TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC	α-IFNα light	Vk3-20*01 (SEQ ID NO: 205)	SEQ ID NO: 21
SEQ ID NO: 113	QVQLQESGPGLVKPSGTLSLTCAVSGGSISSSNW WSWVRQPPGKGLEWIGEIYHSGSTNYNPSLKSRV TISVDKSKNQFSLKLSSVTAADTAVYYCARWTGR TDAFDIWGQGTMVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKRVEPKSCGSSGGGGSGGGGSSGG VFTLEDFVGDWEQTAAYNLDQVLEQGGVSSLLQN LAVSVTPIQRIVRSGENALKIDIHVIIPYEGLSA DQMAQIEEVFKVVYPVDDHHFKVILPYGTLVIDG VTPNMLNYFGRPYEGIAVFDGKKITVTGTLWNGN KIIDERLITPDGSMLFRVTINS	α-IGF1R heavy - LgBiT	VH4-4*01 (SEQ ID NO: 197)	SEQ ID NO: 22
SEQ ID NO: 114	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNG YNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFS GSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPLT FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGECGSSGGGGSGGGGSSGGVTG YRLFEEIL	α-IGF1R light - SmBiT	Vk2-28*01 (SEQ ID NO: 203)	SEQ ID NO: 23
SEQ ID NO: 115	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNG YNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFS GSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPLT FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC	α-IGF1R light	Vk2-28*01 (SEQ ID NO: 203)	SEQ ID NO: 24
SEQ ID NO: 116	EVQLLQSGGGLVQPGGSLRLSCAASGFMFSRYPM HWVRQAPGKGLEWVGSISGSGGATPYADSVKGRF TISRDNSKNTLYLQMNSLRAEDTAVYYCAKDFYQ ILTGNAFDYWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKRVEPKSCGSSGGGGSGGGGS SGGVFTLEDFVGDWEQTAAYNLDQVLEQGGVSSL	α-IGF1R heavy - LgBiT	VH3-23*01 (SEQ ID NO: 191)	SEQ ID NO: 25

	LQNLAVSVTPIQRIVRSGENALKIDIHVIIPYEG LSADQMAQIEEVFKVVYPVDDHHFKVILPYGTLV IDGVTPNMLNYFGRPYEGIAVFDGKKITVTGTLW NGNKIIDERLITPDGSMLFRVTINS			
SEQ ID NO: 117	DIQMTQSPSSLSASLGDRVTITCRASQGISSYLA WYQQKPGKAPKLLIYAKSTLQSGVPSRFSGSGSG TDFTLTISSLQPEDSATYYCQQYWTFPLTFGGGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGECGSSGGGGSGGGGSSGGVTGYRLFE EIL	α-IGF1R light - SmBiT	Vk1-27*01 (SEQ ID NO: 200)	SEQ ID NO: 26
SEQ ID NO: 118	DIQMTQSPSSLSASLGDRVTITCRASQGISSYLA WYQQKPGKAPKLLIYAKSTLQSGVPSRFSGSGSG TDFTLTISSLQPEDSATYYCQQYWTFPLTFGGGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	α-IGF1R light	Vk1-27*01 (SEQ ID NO: 200)	SEQ ID NO: 27
SEQ ID NO: 119	EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSFAM HWVRQAPGKGLEWISVIDTRGATYYADSVKGRFT ISRDNAKNSLYLQMNSLRAEDTAVYYCARLGNFY YGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCGSSGGGGSGGGGSSGGV FTLEDFVGDWEQTAAYNLDQVLEQGGVSSLLQNL AVSVTPIQRIVRSGENALKIDIHVIIPYEGLSAD QMAQIEEVFKVVYPVDDHHFKVILPYGTLVIDGV TPNMLNYFGRPYEGIAVFDGKKITVTGTLWNGNK IIDERLITPDGSMLFRVTINS	α-IGF1R heavy - LgBiT	VH3-21*01 (SEQ ID NO: 190)	SEQ ID NO: 28
SEQ ID NO: 120	EIVLTQSPGTLSVSPGERATLSCRASQSIGSSLH WYQQKPGQAPRLLIKYASQSLSGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCHQSSRLPHTFGQGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGECGSSGGGGSGGGGSSGGVTGYRLFE EIL	α-IGF1R light - SmBiT	Vk3-20*01 (SEQ ID NO: 205)	SEQ ID NO: 29
SEQ ID NO: 121	EIVLTQSPGTLSVSPGERATLSCRASQSIGSSLH WYQQKPGQAPRLLIKYASQSLSGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCHQSSRLPHTFGQGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	α-IGF1R light	Vk3-20*01 (SEQ ID NO: 205)	SEQ ID NO: 30
SEQ ID NO: 122	QVELVESGGGVVQPGRSQRLSCAASGFTFSSYGM HWVRQAPGKGLEWVAIIWFDGSSTYYADSVRGRF TISRDNSKNTLYLQMNSLRAEDTAVYFCARELGR RYFDLWGRGTLVSVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT	α-IGF1R heavy - LgBiT	VH3-33*01 (SEQ ID NO: 193)	SEQ ID NO: 31

	FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCGSSGGGGSGGGGSSGGV FTLEDFVGDWEQTAAYNLDQVLEQGGVSSLLQNL AVSVTPIQRIVRSGENALKIDIHVIIPYEGLSAD QMAQIEEVFKVVYPVDDHHFKVILPYGTLVIDGV TPNMLNYFGRPYEGIAVFDGKKITVTGTLWNGNK IIDERLITPDGSMLFRVTINS			
SEQ ID NO: 123	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDASKRATGIPARFSGSGSG TDFTLTISSLEPEDFAVYYCQQRSKWPPWTFGQG TKVESKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGECGSSGGGGSGGGGSSGGVTGYRLF EEIL	α-IGF1R light - SmBiT	Vk3-11*01 (SEQ ID NO: 204)	SEQ ID NO: 32
SEQ ID NO: 124	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDASKRATGIPARFSGSGSG TDFTLTISSLEPEDFAVYYCQQRSKWPPWTFGQG TKVESKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC	α-IGF1R light	Vk3-11*01 (SEQ ID NO: 204)	SEQ ID NO: 33
SEQ ID NO: 125	EVQLVESGGGLVQPGRSLRLSCAASRFTFDDYAM HWVRQAPGKGLEWVSGISWNSGRIGYADSVKGRF TISRDNAENSLFLQMNGLRAEDTALYYCAKGRDS FDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKRVEPKSCGSSGGGGSGGGGSSGGVFT LEDFVGDWEQTAAYNLDQVLEQGGVSSLLQNLAV SVTPIQRIVRSGENALKIDIHVIIPYEGLSADQM AQIEEVFKVVYPVDDHHFKVILPYGTLVIDGVTP NMLNYFGRPYEGIAVFDGKKITVTGTLWNGNKII DERLITPDGSMLFRVTINS	α-IL6R heavy - LgBiT	VH3-9*01 (SEQ ID NO: 196)	SEQ ID NO: 34
SEQ ID NO: 126	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLA WYQQKPGKAPKLLIYGASSLESGVPSRFSGSGSG TDFTLTISSLQPEDFASYYCQQANSFPYTFGQGT KLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGECGSSGGGGSGGGGSSGGVTGYRLFE EIL	α-IL6R light - SmBiT	Vk1-12*01 (SEQ ID NO: 199)	SEQ ID NO: 35
SEQ ID NO: 127	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLA WYQQKPGKAPKLLIYGASSLESGVPSRFSGSGSG TDFTLTISSLQPEDFASYYCQQANSFPYTFGQGT KLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	α-IL6R light	Vk1-12*01 (SEQ ID NO: 199)	SEQ ID NO: 36
SEQ ID NO:	EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYEM KWVRQAPGKGLEWVSVIGPSGGFTFYADSVKGRF	α-LINGO-1 heavy –	VH3-23*01	SEQ ID NO: 37

128	TISRDNSKNTLYLQMNSLRAEDTAVYYCATEGDN DAFDIWGQGTTVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCGSSGGGGSGGGGSSGGV FTLEDFVGDWEQTAAYNLDQVLEQGGVSSLLQNL AVSVTPIQRIVRSGENALKIDIHVIIPYEGLSAD QMAQIEEVFKVVYPVDDHHFKVILPYGTLVIDGV TPNMLNYFGRPYEGIAVFDGKKITVTGTLWNGNK IIDERLITPDGSMLFRVTINS	LgBiT	(SEQ ID NO: 191)	
SEQ ID NO: 129	DIQMTQSPATLSLSPGERATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDASNRATGIPARFSGSGSG TDFTLTISSLEPEDFAVYYCQQRSNWPMYTFGQG TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGECGSSGGGGSGGGGSSGGVTGYRLF EEIL	α-LINGO-1 light - SmBiT	Vk3-11*01 (SEQ ID NO: 204)	SEQ ID NO: 38
SEQ ID NO: 130	DIQMTQSPATLSLSPGERATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDASNRATGIPARFSGSGSG TDFTLTISSLEPEDFAVYYCQQRSNWPMYTFGQG TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC	α-LINGO-1 light	Vk3-11*01 (SEQ ID NO: 204)	SEQ ID NO: 39
SEQ ID NO: 131	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAM SWVRQAPGKGLEWVSQISPAGGYTNYADSVKGRF TISADTSKNTAYLQMNSLRAEDTAVYYCARGELP YYRMSKVMDVWGQGTLVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKRVEPKSCGSSGGGGSGGGG SSGGVFTLEDFVGDWEQTAAYNLDQVLEQGGVSS LLQNLAVSVTPIQRIVRSGENALKIDIHVIIPYE GLSADQMAQIEEVFKVVYPVDDHHFKVILPYGTL VIDGVTPNMLNYFGRPYEGIAVFDGKKITVTGTL WNGNKIIDERLITPDGSMLFRVTINS	α-neuropilin 1 heavy - LgBiT	VH3-66*01 (SEQ ID NO: 194)	SEQ ID NO: 40
SEQ ID NO: 132	DIQMTQSPSSLSASVGDRVTITCRASQYFSSYLA WYQQKPGKAPKLLIYGASSRASGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQYLGSPPTFGQGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGECGSSGGGGSGGGGSSGGVTGYRLFE EIL	α-neuropilin 1 light - SmBiT	Vk1-39*01 (SEQ ID NO: 201)	SEQ ID NO: 41
SEQ ID NO: 133	DIQMTQSPSSLSASVGDRVTITCRASQYFSSYLA WYQQKPGKAPKLLIYGASSRASGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQYLGSPPTFGQGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP	α-neuropilin 1 light	Vk1-39*01 (SEQ ID NO: 201)	SEQ ID NO: 42

	VTKSFNRGEC			
SEQ ID NO: 134	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAI SWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRV TITADKSTSTAYMELSSLRSEDTAVYYCARAPLR FLEWSTQDHYYYYYMDVWGKGTTVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKRVEPKSCGSSGG GGSGGGGSSGGVFTLEDFVGDWEQTAAYNLDQVL EQGGVSSLLQNLAVSVTPIQRIVRSGENALKIDI HVIIPYEGLSADQMAQIEEVFKVVYPVDDHHFKV ILPYGTLVIDGVTPNMLNYFGRPYEGIAVFDGKK ITVTGTLWNGNKIIDERLITPDGSMLFRVTINS	α-CD221 heavy - LgBiT	VH1-69*01 (SEQ ID NO: 187)	SEQ ID NO: 43
SEQ ID NO: 135	SSELTQDPAVSVALGQTVRITCQGDSLRSYYATW YQQKPGQAPILVIYGENKRPSGIPDRFSGSSSGN TASLTITGAQAEDEADYYCKSRDGSGQHLVFGGG TKLTVLGQPKANPTVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADGSPVKAGVETTKPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPTECSGSSGGGGSGGGGSSGGVTGYRLFE EIL	α-CD221 light - SmBiT	Vl3-19*01 (SEQ ID NO: 211)	SEQ ID NO: 44
SEQ ID NO: 136	SSELTQDPAVSVALGQTVRITCQGDSLRSYYATW YQQKPGQAPILVIYGENKRPSGIPDRFSGSSSGN TASLTITGAQAEDEADYYCKSRDGSGQHLVFGGG TKLTVLGQPKANPTVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADGSPVKAGVETTKPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPTECS	α-CD221 light	Vl3-19*01 (SEQ ID NO: 211)	SEQ ID NO: 45
SEQ ID NO: 137	EVQLVQSGGGVERPGGSLRLSCAASGFTFDDYAM SWVRQAPGKGLEWVSGINWQGGSTGYADSVKGRV TISRDNAKNSLYLQMNSLRAEDTAVYYCAKILGA GRGWYFDYWGKGTTVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKRVEPKSCGSSGGGGSGGGGSS GGVFTLEDFVGDWEQTAAYNLDQVLEQGGVSSLL QNLAVSVTPIQRIVRSGENALKIDIHVIIPYEGL SADQMAQIEEVFKVVYPVDDHHFKVILPYGTLVI DGVTPNMLNYFGRPYEGIAVFDGKKITVTGTLWN GNKIIDERLITPDGSMLFRVTINS	α-death receptor 5 heavy - LgBiT	VH3-20*01 (SEQ ID NO: 189)	SEQ ID NO: 46
SEQ ID NO: 138	SSELTQDPAVSVALGQTVRITCSGDSLRSYYASW YQQKPGQAPVLVIYGANNRPSGIPDRFSGSSSGN TASLTITGAQAEDEADYYCNSADSSGNHVVFGGG TKLTVLGQPKANPTVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADGSPVKAGVETTKPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPTECSGSSGGGGSGGGGSSGGVTGYRLFE EIL	α-death receptor 5 light - SmBiT	Vl3-19*01 (SEQ ID NO: 211)	SEQ ID NO: 47
SEQ ID NO: 139	SSELTQDPAVSVALGQTVRITCSGDSLRSYYASW YQQKPGQAPVLVIYGANNRPSGIPDRFSGSSSGN TASLTITGAQAEDEADYYCNSADSSGNHVVFGGG	α-death receptor 5 light	Vl3-19*01 (SEQ ID	SEQ ID NO: 48

	TKLTVLGQPKANPTVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADGSPVKAGVETTKPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPTECS		NO: 211)	
SEQ ID NO: 140	EVQLVQSGAEVKKPGESLKISCKGSGYSFSNYWI GWVRQMPGKGLEWMGIIDPSNSYTRYSPSFQGQV TISADKSISTAYLQWSSLKASDTAMYYCARWYYK PFDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKRVEPKSCGSSGGGGSGGGGSSGGVF TLEDFVGDWEQTAAYNLDQVLEQGGVSSLLQNLA VSVTPIQRIVRSGENALKIDIHVIIPYEGLSADQ MAQIEEVFKVVYPVDDHHFKVILPYGTLVIDGVT PNMLNYFGRPYEGIAVFDGKKITVTGTLWNGNKI IDERLITPDGSMLFRVTINS	α-IL23 heavy - LgBiT	VH5-51*01 (SEQ ID NO: 198)	SEQ ID NO: 49
SEQ ID NO: 141	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGSGYD VHWYQQLPGTAPKLLIYGNSKRPSGVPDRFSGSK SGTSASLAITGLQSEDEADYYCASWTDGLSLVVF GGGTKLTVLGQPKANPTVTLFPPSSEELQANKAT LVCLISDFYPGAVTVAWKADGSPVKAGVETTKPS KQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG STVEKTVAPTECSGSSGGGGSGGGGSSGGVTGYR LFEEIL	α-IL23 light - SmBiT	Vl1-40*01 (SEQ ID NO: 208)	SEQ ID NO: 50
SEQ ID NO: 142	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGSGYD VHWYQQLPGTAPKLLIYGNSKRPSGVPDRFSGSK SGTSASLAITGLQSEDEADYYCASWTDGLSLVVF GGGTKLTVLGQPKANPTVTLFPPSSEELQANKAT LVCLISDFYPGAVTVAWKADGSPVKAGVETTKPS KQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG STVEKTVAPTECS	α-IL23 light	Vl1-40*01 (SEQ ID NO: 208)	SEQ ID NO: 51
SEQ ID NO: 143	QVQLVQSGGGLVQPGGSLRLSCAASGFTFDDYAM HWVRQAPGKGLEWVAGISWDSGSTGYADSVKGRF TISRDNAKNSLYLQMNSLRAEDTALYYCARDLGA YQWVEGFDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKRVEPKSCGSSGGGGSGGGGS SGGVFTLEDFVGDWEQTAAYNLDQVLEQGGVSSL LQNLAVSVTPIQRIVRSGENALKIDIHVIIPYEG LSADQMAQIEEVFKVVYPVDDHHFKVILPYGTLV IDGVTPNMLNYFGRPYEGIAVFDGKKITVTGTLW NGNKIIDERLITPDGSMLFRVTINS	α-HER3 heavy - LgBiT	VH3-9*01 (SEQ ID NO: 196)	SEQ ID NO: 52
SEQ ID NO: 144	SYELTQDPAVSVALGQTVRITCQGDSLRSYYASW YQQKPGQAPVLVIYGKNNRPSGIPDRFSGSTSGN SASLTITGAQAEDEADYYCNSRDSPGNQWVFGGG TKVTVLGGQPKANPTVTLFPPSSEELQANKATLV CLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQ SNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGST VEKTVAPTECSGSSGGGGSGGGGSSGGVTGYRLF EEIL	α-HER3 light - SmBiT	Vl3-19*01 (SEQ ID NO: 211)	SEQ ID NO: 53

SEQ ID NO: 145	SYELTQDPAVSVALGQTVRITCQGDSLRSYYASW YQQKPGQAPVLVIYGKNNRPSGIPDRFSGSTSGN SASLTITGAQAEDEADYYCNSRDSPGNQWVFGGG TKVTVLGGQPKANPTVTLFPPSSEELQANKATLV CLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQ SNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGST VEKTVAPTECS	α-HER3 light	Vl3-19*01 (SEQ ID NO: 211)	SEQ ID NO: 54
SEQ ID NO: 146	EVQLVQSGGGVERPGGSLRLSCAASGFTFDDYGM SWVRQAPGKGLEWVSGINWNGGSTGYADSVKGRV TISRDNAKNSLYLQMNSLRAEDTAVYYCAKILGA GRGWYFDLWGKGTTVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKRVEPKSCGSSGGGGSGGGGSS GGVFTLEDFVGDWEQTAAYNLDQVLEQGGVSSLL QNLAVSVTPIQRIVRSGENALKIDIHVIIPYEGL SADQMAQIEEVFKVVYPVDDHHFKVILPYGTLVI DGVTPNMLNYFGRPYEGIAVFDGKKITVTGTLWN GNKIIDERLITPDGSMLFRVTINS	α-TRAILR2 heavy - LgBiT	VH3-20*01 (SEQ ID NO: 189)	SEQ ID NO: 55
SEQ ID NO: 147	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASW YQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGN TASLTITGAQAEDEADYYCNSRDSSGNHVVFGGG TKLTVLGQPKANPTVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADGSPVKAGVETTKPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPTECSGSSGGGGSGGGGSSGGVTGYRLFE EIL	α-TRAILR2 light - SmBiT	Vl3-19*01 (SEQ ID NO: 211)	SEQ ID NO: 56
SEQ ID NO: 148	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASW YQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGN TASLTITGAQAEDEADYYCNSRDSSGNHVVFGGG TKLTVLGQPKANPTVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADGSPVKAGVETTKPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPTECS	α-TRAILR2 light	Vl3-19*01 (SEQ ID NO: 211)	SEQ ID NO: 57
SEQ ID NO: 149	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSSYI NWVRQAPGQGLEWMGTINPVSGSTSYAQKFQGRV TMTRDTSISTAYMELSRLRSDDTAVYYCARGGWF DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKRVEPKSCGSSGGGGSGGGGSSGGVFTL EDFVGDWEQTAAYNLDQVLEQGGVSSLLQNLAVS VTPIQRIVRSGENALKIDIHVIIPYEGLSADQMA QIEEVFKVVYPVDDHHFKVILPYGTLVIDGVTPN MLNYFGRPYEGIAVFDGKKITVTGTLWNGNKIID ERLITPDGSMLFRVTINS	α-activin receptors heavy - LgBiT	VH1-46*01 (SEQ ID NO: 186)	SEQ ID NO: 58
SEQ ID NO: 150	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNY VNWYQQHPGKAPKLMIYGVSKRPSGVSNRFSGSK SGNTASLTISGLQAEDEADYYCGTFAGGSYYGVF GGGTKLTVLGQPKANPTVTLFPPSSEELQANKAT LVCLISDFYPGAVTVAWKADGSPVKAGVETTKPS	α-activin receptors light - SmBiT	Vl2-14*01 (SEQ ID NO: 210)	SEQ ID NO: 59

	KQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG STVEKTVAPTECSGSSGGGGSGGGGSSGGVTGYR LFEEIL			
SEQ ID NO: 151	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNY VNWYQQHPGKAPKLMIYGVSKRPSGVSNRFSGSK SGNTASLTISGLQAEDEADYYCGTFAGGSYYGVF GGGTKLTVLGQPKANPTVTLFPPSSEELQANKAT LVCLISDFYPGAVTVAWKADGSPVKAGVETTKPS KQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG STVEKTVAPTECS	α-activin receptors light	Vl2-14*01 (SEQ ID NO: 210)	SEQ ID NO: 60
SEQ ID NO: 152	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAI SWVRQAPGQGLEWMGGIGPFFGTANYAQKFQGRV TITADESTSTAYMELSSLRSEDTAVYYCARDTPY FDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKRVEPKSCGSSGGGGSGGGGSSGGVFT LEDFVGDWEQTAAYNLDQVLEQGGVSSLLQNLAV SVTPIQRIVRSGENALKIDIHVIIPYEGLSADQM AQIEEVFKVVYPVDDHHFKVILPYGTLVIDGVTP NMLNYFGRPYEGIAVFDGKKITVTGTLWNGNKII DERLITPDGSMLFRVTINS	α-complement C5 heavy - LgBiT	VH1-69*01 (SEQ ID NO: 187)	SEQ ID NO: 61
SEQ ID NO: 153	SYELTQPLSVSVALGQTARITCSGDSIPNYYVYW YQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGN TATLTISRAQAGDEADYYCQSFDSSLNAEVFGGG TKLTVLGQPKANPTVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADGSPVKAGVETTKPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPTECSGSSGGGGSGGGGSSGGVTGYRLFE EIL	α-complement C5 light - SmBiT	Vl3-9*01 (SEQ ID NO: 212)	SEQ ID NO: 62
SEQ ID NO: 154	SYELTQPLSVSVALGQTARITCSGDSIPNYYVYW YQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGN TATLTISRAQAGDEADYYCQSFDSSLNAEVFGGG TKLTVLGQPKANPTVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADGSPVKAGVETTKPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPTECS	α-complement C5 light	Vl3-9*01 (SEQ ID NO: 212)	SEQ ID NO: 63
SEQ ID NO: 155	EVQLVQSGAEVKKPGASVKVSCKASGYTFTGYHM HWVRQAPGQGLEWMGWINPNSGVTKYAQKFQGRV TMTRDTSINTAYMELSRLRFDDTDVYYCATGGFG YWGEGTLVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKRVEPKSCGSSGGGGSGGGGSSGGVFTLE DFVGDWEQTAAYNLDQVLEQGGVSSLLQNLAVSV TPIQRIVRSGENALKIDIHVIIPYEGLSADQMAQ IEEVFKVVYPVDDHHFKVILPYGTLVIDGVTPNM LNYFGRPYEGIAVFDGKKITVTGTLWNGNKIIDE RLITPDGSMLFRVTINS	α-CCR2 heavy - LgBiT	VH1-2*01 (SEQ ID NO: 184)	SEQ ID NO: 64
SEQ ID NO:	LPVLTQPPSVSKGLRQTATLTCTGNSNNVGNQGA AWLQQHQGQPPKLLSYRNHNRPSGVSERFSPSRS	α-CCR2 light -	Vl10-54*01	SEQ ID NO: 65

156	GDTSSLTITGLQPEDEADYYCLAWDSSLRAFVFG TGTKLTVLGQPKANPTVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADGSPVKAGVETTKPSK QSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS TVEKTVAPTECSGSSGGGGSGGGGSSGGVTGYRL FEEIL	SmBiT	(SEQ ID NO: 207)	
SEQ ID NO: 157	LPVLTQPPSVSKGLRQTATLTCTGNSNNVGNQGA AWLQQHQGQPPKLLSYRNHNRPSGVSERFSPSRS GDTSSLTITGLQPEDEADYYCLAWDSSLRAFVFG TGTKLTVLGQPKANPTVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADGSPVKAGVETTKPSK QSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS TVEKTVAPTECS	α-CCR2 light	Vl10-54*01 (SEQ ID NO: 207)	SEQ ID NO: 66
SEQ ID NO: 158	EVQLVESGGGLVQPGGSLRLSCVASGFTFSDYWM SWVRQAPGKGLEWVANIKKDGSVNYYVDSVKGRF TISRDNAKNSLYLQMNSLRAEDTAVYYCTRFDYW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCGSSGGGGSGGGGSSGGVFTLEDF VGDWEQTAAYNLDQVLEQGGVSSLLQNLAVSVTP IQRIVRSGENALKIDIHVIIPYEGLSADQMAQIE EVFKVVYPVDDHHFKVILPYGTLVIDGVTPNMLN YFGRPYEGIAVFDGKKITVTGTLWNGNKIIDERL ITPDGSMLFRVTINS	α-CCR2 heavy - LgBiT	VH3-7*01 (SEQ ID NO: 195)	SEQ ID NO: 67
SEQ ID NO: 159	QAGLTQPPSVSKGLRQTATLTCTGNSNNVGNQGA AWLQQHQGHPPKLLFYRNNNRASGISERLSASRS GNTASLTITGLQPEDEADYYCLTWDSSLSVVVFG GGTKLTVLGQPKANPTVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADGSPVKAGVETTKPSK QSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS TVEKTVAPTECSGSSGGGGSGGGGSSGGVTGYRL FEEIL	α-CCR2 light - SmBiT	Vl10-54*01 (SEQ ID NO: 207)	SEQ ID NO: 68
SEQ ID NO: 160	QAGLTQPPSVSKGLRQTATLTCTGNSNNVGNQGA AWLQQHQGHPPKLLFYRNNNRASGISERLSASRS GNTASLTITGLQPEDEADYYCLTWDSSLSVVVFG GGTKLTVLGQPKANPTVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADGSPVKAGVETTKPSK QSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS TVEKTVAPTECS	α-CCR2 light	Vl10-54*01 (SEQ ID NO: 207)	SEQ ID NO: 69
SEQ ID NO: 161	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGM HWVRQAPGKGLEWVAFIRYDGSNKYYADSVKGRF TISRDNSKNTLYLQMNSLRAEDTAVYYCKTHGSH DNWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKRVEPKSCGSSGGGGSGGGGSSGGVFTL EDFVGDWEQTAAYNLDQVLEQGGVSSLLQNLAVS VTPIQRIVRSGENALKIDIHVIIPYEGLSADQMA QIEEVFKVVYPVDDHHFKVILPYGTLVIDGVTPN MLNYFGRPYEGIAVFDGKKITVTGTLWNGNKIID	α-IL12β heavy - LgBiT	VH3-33*01 (SEQ ID NO: 193)	SEQ ID NO: 70

	ERLITPDGSMLFRVTINS			
SEQ ID NO: 162	QSVLTQPPSVSGAPGQRVTISCSGSRSNIGSNTV KWYQQLPGTAPKLLIYYNDQRPSGVPDRFSGSKS GTSASLAITGLQAEDEADYYCQSYDRYTHPALLF GTGTKVTVLGQPKANPTVTLFPPSSEELQANKAT LVCLISDFYPGAVTVAWKADGSPVKAGVETTKPS KQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG STVEKTVAPTECSGSSGGGGSGGGGSSGGVTGYR LFEEIL	α-IL12β light - SmBiT	Vl1-44*01 (SEQ ID NO: 209)	SEQ ID NO: 71
SEQ ID NO: 163	QSVLTQPPSVSGAPGQRVTISCSGSRSNIGSNTV KWYQQLPGTAPKLLIYYNDQRPSGVPDRFSGSKS GTSASLAITGLQAEDEADYYCQSYDRYTHPALLF GTGTKVTVLGQPKANPTVTLFPPSSEELQANKAT LVCLISDFYPGAVTVAWKADGSPVKAGVETTKPS KQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG STVEKTVAPTECS	α-IL12β light	Vl1-44*01 (SEQ ID NO: 209)	SEQ ID NO: 72

3. NanoBiT competition assay.

First, a NanoBiT assay was conducted to test the binding between a heavy chain polypeptide (HCP2) and its cognate kappa light chain polypeptide (KLCP) in the presence of a competing lambda light chain polypeptide (LLCP). As shown in **FIGs. 3A-3C**, a LgBiT was fused to the C-terminus of the HCP2 and a SmBiT was fused to the C-terminus of the KLCP. The competing LLCP was expressed as an un-modified chain. When HCP2 and KLCP form a Fab, the LgBiT and SmBiT generate a fully functional NanoLuc domain, which has luciferase activity (**FIG. 3A**). When HCP2 and LLCP form a Fab, the NanoLuc is not complete and is inactive (**FIG. 3B**). A 1:1:1 competition of LLCP and KLCP for HCP2 results in the HCP2/KLCP Fab with a functional NanoLuc and the HCP2/LLCP Fab with a nonfunctional NanoLuc (**FIG. 3C**). Each testing included a positive control where the competing light chain was absent, as well as a negative control where the competing light chain was the same KLCP without the SmBiT fusion. The positive control represented 100 % pairing; whereas, the negative control represented 50 % pairing. The luminescence readings for the positive and negative controls (100 % and 50 %, respectively) and the luminescence readings for each test pair in the presence of a competing light chain, were compared to quantify the percent pairing for each test pair.

A similar NanoBiT assay was used to test the binding between a heavy chain polypeptide (HCP1) and a lambda light chain polypeptide (LLCP) in the presence of a competing kappa chain polypeptide (KLCP) (**FIGs. 4A-4C**). In this assay, a LgBiT was fused to the C-

terminus of the HCP1 and a SmBiT was fused to the C-terminus of the LLCP. The competing KLCP was expressed as an un-modified light chain. Expression of the HCP1, LLCP, and KLCP at 1:1:1 leads to formation of the HCP1/LLCP Fab with a functional NanoLuc, and the HCP1/KLCP Fab with a nonfunctional NanoLuc (**FIG. 4C**). Similarly, luminescence readings for each test pair in the presence of a competing light chain were compared with those for positive controls (the competing light chain was absent; 100% pairing) and negative controls (the competing light chain was the same LLCP without the SmBiT fusion; 50% pairing) to determine the percent pairing for each test pair.

The NanoBiT competition assays were performed with 100 µL of protein at 1 µg/mL in 96 well plates. A 5x stock solution was made of the Promega Nano-Glo (N1110) assay system following the manufacturer's instructions. Each well received 20 µL of 5x NanoLuc stock solution and the luminescence of the plate was immediately read using a SpectraMax i3x plate reader.

4. Expression and purification of multispecific molecules.

The plasmids were co-transfected into either Expi293 cells (Life Technologies A14527) or ExpiCHO cells (Life Technologies A29127). Transfections were performed using 1 mg of total DNA for a multispecific construct with a 1:1 knob to hole heavy chain ratio and 3:2 light chain to heavy chain ratio. To investigate possible misbalance in expression of the chains, the transfections were performed using varying ratios of heavy chain ranging from 3:1 to 1:3 of knob to hole heavy chain DNA, with the same 3:2 light chain to heavy chain ratio. Transfection in Expi293 cells was done using linear 25,000 Da polyethylenimine (PEI, Polysciences Inc 23966) in a 3:1 ratio with the total DNA. The DNA and PEI were each added to 50 mL of OptiMem (Life Technologies 31985088) medium and sterile filtered. The DNA and PEI were combined for 10 minutes and added to the Expi293 cells with a cell density of 1.8 – 2.8 x 10^6 cells/mL and a viability of at least 95%. The ExpiCHO transfection was performed according to the manufacturer's instructions. Expi293 cells were grown in a humidified incubator at 37 °C with 8 % CO_2 for 5-7 days after transfection and ExpiCHO cells were grown for 14 days at 32 °C with 5 % CO_2. The cells were pelleted by centrifugation at 18,000 x g and the supernatant was filtered through a 0.2 µm membrane. Protein A resin (GE 17-1279-03) was added to the filtered supernatant and incubated for 1-3 hours at room temperature. The resin was packed into a

column, washed with 3 x 10 column volumes of Dulbecco's phosphate-buffered saline (DPBS, Life Technologies 14190-144). The bound protein was eluted from the column with 20 mM citrate, 100 mM NaCl, pH 2.9. When necessary, the proteins were further purified using size exclusion chromatography on a Superdex 200 column with a running buffer of DPBS.

Table 4 contains the sequences unique to the multispecific constructs. Some of the light chain sequences shown in Table 2 were also used to express the multispecific constructs. A total of 12 multispecific molecules were expressed as described above. The amino acid sequences of these molecules are provided in Table 5a. Table 5b provides the corresponding germline sequences for the multispecific molecules.

Table 4. Amino acid sequences used to construct multispecific constructs.

SEQ ID NO	Amino Acid Sequence	Description	Germline	Corresponding DNA SEQ ID NO
SEQ ID NO: 164	QVQLQESGPGLVKPSQTLSLTCTVSGGSINNNNYY WTWIRQHPGKGLEWIGYIYYSGSTFYNPSLKSRVT ISVDTSKTQFSLKLSSVTAADTAVYYCAREDTMTG LDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPCREEMTKNQVSLWCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	α-mesothelin AB237 heavy - hCHIg_Knob_Cys	VH4-31*01 (SEQ ID NO: 213)	SEQ ID NO: 82
SEQ ID NO: 165	DIQMTQSPSSLSASVGDRVTITCRASQSINNYLNW YQQKPGKAPTLLIYAASSLQSGVPSRFSGSRSGTD FTLTISSLQPEDFAAYFCQQTYSNPTFGQGTKVEV KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC	α-mesothelin AB237 light - hCLIg_vk	Vk1-39*01 (SEQ ID NO: 201)	SEQ ID NO: 83
SEQ ID NO: 166	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMM WVRQAPGKGLEWVSSIYPSGGITFYADTVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCARIKLGTVT TVDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ	α-PDL1 heavy - hCHIg_Hole_Cys	VH3-66*01 (SEQ ID NO: 194)	SEQ ID NO: 84

	VCTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK			
SEQ ID NO: 167	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYV SWYQQHPGKAPKLMIYDVSNRPSGVSNRFSGSKSG NTASLTISGLQAEDEADYYCSSYTSSSTRVFGTGT KVTVLGQPKANPTVTLFPPSSEELQANKATLVCLI SDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTV APTECS	α-PDL1 light - hCLIg_vl	Vl2-14*01 (SEQ ID NO: 210)	SEQ ID NO: 85
SEQ ID NO: 168	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMH WVRQAPGKGLEWVTFISYDGNNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPF DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPCREEMTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	α-CTLA4 heavy - hCHIg_Knob_Cys	VH3-30*01 (SEQ ID NO: 192)	SEQ ID NO: 78
SEQ ID NO: 169	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMH WVRQAPGKGLEWVTFISYDGNNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPF DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPCREEMTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGG GGSGGGGSEVQLVESGGGLVKPGGSLRLSCAASGF TFSPYSVFWVRQAPGKGLEWVSSINTDSTYKYYAD SVKGRFTISRDNAENSIFLQMNSLRAEDTAVYYCA RDRSYYAFSSGSLSDYYYGLDVWGQGTLVTVSSGG GGSGGGGSGGGGSGGGGSDIVMTQSPLSLSVTPGE PASISCRSSQSLLHTNLYNYLDWYVQKPGQSPQLL IYLASNRASGVPDRFSGSGSGTDFTLKISRVETED VGVYYCMQALQIPRTFGQGTKLEIK	α-CTLA4 heavy - hCHIg_Knob_Cys - GH_scFv	VH3-30*01 (SEQ ID NO: 192)	SEQ ID NO: 79
SEQ ID NO: 170	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMH WVRQAPGKGLEWVAFIRYDGSNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCKTHGSHDNW GQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP	α-IL12β heavy - hCHIg_Hole_Cys	VH3-33*01 (SEQ ID NO: 193)	SEQ ID NO: 91

	KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLP PSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK			
SEQ ID NO: 171	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMH WVRQAPGKGLEWVTFISYDGNNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPF DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	α-CTLA4 heavy - hCHIg	VH3-30*01 (SEQ ID NO: 192)	SEQ ID NO: 73
SEQ ID NO: 172	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMH WVRQAPGKGLEWVAFIRYDGSNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCKTHGSHDNW GQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK	α-IL12β heavy - hCHIg	VH3-33*01 (SEQ ID NO: 193)	SEQ ID NO: 74
SEQ ID NO: 173	QSVLTQPPSVSGAPGQRVTISCSGSRSNIGSNTVK WYQQLPGTAPKLLIYYNDQRPSGVPDRFSGSKSGT SASLAITGLQAEDEADYYCQSYDRYTHPALLFGTG TKVTVLGQPKANPTVTLFPPSSEELQANKATLVCL ISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKT VAPTECSGGGGSGGGGSGGGGSAPTSSSTKKTQLQ LEHLLLDLQMILNGINNYKNPKLTRMLTAKFAMPK KATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETATIVEFL NRWITFCQSIISTLT	α-IL12β light - hCLIg_vl - IL2	Vl1-44*01 (SEQ ID NO: 209)	SEQ ID NO: 75
SEQ ID NO: 174	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMH WVRQAPGKGLEWVAFIRYDGSNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCKTHGSHDNW GQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV	α-IL12β heavy - hCHIg_Hole_Cys	VH3-33*01 (SEQ ID NO: 193)	SEQ ID NO: 76

	EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLP PSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGS GGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINN YKNPKLTRMLTAKFAMPKKATELKHLQCLEEELKP LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFCQSIISTLT			
SEQ ID NO: 175	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMH WVRQAPGKGLEWVAFIRYDGSNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCKTHGSHDNW GQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGS GGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINN YKNPKLTRMLTAKFAMPKKATELKHLQCLEEELKP LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFCQSIISTLT	α-IL12β heavy - hCHIg	VH3-33*01 (SEQ ID NO: 193)	SEQ ID NO: 77
SEQ ID NO: 176	EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYLA WYQQKPGQAPRLLIYGAFSRATGIPDRFSGSGSGT DFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKV EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGECGGGGSGGGGSGGGGSAPTSSSTKKTQLQLE HLLLDLQMILNGINNYKNPKLTRMLTAKFAMPKKA TELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDL ISNINVIVLELKGSETTFMCEYADETATIVEFLNR WITFCQSIISTLT	α-CTLA4 light - hCLIg_vk - IL2	Vk3-20*01 (SEQ ID NO: 205)	SEQ ID NO: 80
SEQ ID NO: 177	EVQLVQSGGGVERPGGSLRLSCAASGFTFDDYGMS WVRQAPGKGLEWVSGINWNGGSTGYADSVKGRVTI SRDNAKNSLYLQMNSLRAEDTAVYYCAKILGAGRG WYFDLWGKGTTVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVCTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	α-TNFR10β heavy - hCHIg_Hole_Cys	Vk3-20*01 (SEQ ID NO: 205)	SEQ ID NO: 81
SEQ	QVQLVQSGGGLVQPGGSLRLSCAASGFTFDDYAMH	α-HER3	VH3-	SEQ ID NO:

ID NO: 178	WVRQAPGKGLEWVAGISWDSGSTGYADSVKGRFTI SRDNAKNSLYLQMNSLRAEDTALYYCARDLGAYQW VEGFDYWGQGTLVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKRVEPKSCTIKPCPPCKCPAPNLLGGPS VFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQ ISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQ HQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVR APQVYVLPPCEEEMTKKQVTLWCMVTDFMPEDIYV EWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEK KNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK	heavy - mFc_Knob _Cys	9*01 (SEQ ID NO: 196)	86
SEQ ID NO: 179	EVQLLQSGGGLVQPGGSLRLSCAASGFMFSRYPMH WVRQAPGKGLEWVGSISGSGGATPYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCAKDFYQILT GNAFDYWGQGTTVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKRVEPKSCTIKPCPPCKCPAPNLLGGPS VFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQ ISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQ HQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVR APQVCVLPPPEEEMTKKQVTLSCAVTDFMPEDIYV EWTNNGKTELNYKNTEPVLDSDGSYFMVSKLRVEK KNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK	α-IGF1R heavy - mFc_Hole_ Cys	VH3-23*01 (SEQ ID NO: 191)	SEQ ID NO: 87
SEQ ID NO: 180	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAIS WVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTI TADKSTSTAYMELSSLRSEDTAVYYCARAPLRFLE WSTQDHYYYYYMDVWGKGTTVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVCTLPPSREEMTKNQVSLSCAVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLV SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK	α-CD221 heavy - hCHIg_Hol e_Cys	VH1-69*01 (SEQ ID NO: 187)	SEQ ID NO: 88
SEQ ID NO: 181	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMH WVRQAPGKGLEWVAVIWYDGSKRYYADSVKGRFTI SRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQ GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPC REEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS	α-PD1 heavy - hCHIg_Kn ob_Cys	VH3-33*01 (SEQ ID NO: 193)	SEQ ID NO: 89

	CSVMHEALHNHYTQKSLSLSPGK			
SEQ ID NO: 182	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAW YQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTD FTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	α-PD1 light - hCLIg_vk	Vk3-11*01 (SEQ ID NO: 204)	SEQ ID NO: 90

Table 15. Germline sequences shown in Tables 2 and 4 (full-length sequences).

SEQ ID NO	**Description**	**Amino acid sequences**
183	VH1-18*01	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNGN TNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR
184	VH1-2*01	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGRINPNSGG TNYAQKFQGRVTSTRDTSISTAYMELSRLRSDDTVVYYCAR
185	VH1-3*01	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYAMHWVRQAPGQRLEWMGWINAGNGN TKYSQKFQGRVTITRDTSASTAYMELSSLRSEDTAVYYCAR
186	VH1-46*01	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGS TSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
187	VH1-69*01	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGT ANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAR
188	VH3-13*01	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYDMHWVRQATGKGLEWVSAIGTAGDT YYPGSVKGRFTISRENAKNSLYLQMNSLRAGDTAVYYCAR
189	VH3-20*01	EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSGINWNGGS TGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYHCAR
190	VH3-21*01	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSY IYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR
191	VH3-23*01	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGS TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK
192	VH3-30*01	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSN KYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
193	VH3-33*01	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSN KYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
194	VH3-66*01	EVQLVESGGGLVQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLEWVSVIYSGGST YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
195	VH3-7*01	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQDGSE KYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR
196	VH3-9*01	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGS IGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAK
197	VH4-4*01	QVQLQESGPGLVKPPGTLSLTCAVSGGSISSSNWWSWVRQPPGKGLEWIGEIYHSGS TNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYCCAR
198	VH5-51*01	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSD TRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCAR
199	Vk1-12*01	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYC

200	Vk1-27*01	DIQMTQSPSSLSASVGDRVTITCRASQGISNYLAWYQQKPGKVPKLLIYAASTLQSG VPSRFSGSGSGTDFTLTISSLQPEDVATYYC
201	Vk1-39*01	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYC
202	Vk1D-16*01	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYC
203	Vk2-28*01	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGS NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC
204	Vk3-11*01	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATG IPARFSGSGSGTDFTLTISSLEPEDFAVYYC
205	Vk3-20*01	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRAT GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC
206	Vk3D-20*01	EIVLTQSPATLSLSPGERATLSCGASQSVSSSYLAWYQQKPGLAPRLLIYDASSRAT GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC
207	Vl10-54*01	QAGLTQPPSVSKGLRQTATLTCTGNSNNVGNQGAAWLQQHQGHPPKLLSYRNNNRPS GISERLSASRSGNTASLTITGLQPEDEADYYC
208	Vl1-40*01	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRP SGVPDRFSGSKSGTSASLAITGLQAEDEADYYC
209	Vl1-44*01	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPS GVPDRFSGSKSGTSASLAISGLQSEDEADYYC
210	Vl2-14*01	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSNRP SGVSNRFSGSKSGNTASLTISGLQAEDEADYYC
211	Vl3-19*01	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGI PDRFSGSSSGNTASLTITGAQAEDEADYYC
212	Vl3-9*01	SYELTQPLSVSVALGQTARITCGGNNIGSKNVHWYQQKPGQAPVLVIYRDSNRPSGI PERFSGSNSGNTATLTISRAQAGDEADYYC
213	VH4-31*01	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGLEWIGYIYYSG STYYNPSLKSLVTISVDTSKNQFSLKLSSVTAADTAVYYCAR

Table 16. Germline sequences shown in Tables 2 and 4 (framework 1, CDR1, framework 2, CDR2, and framework 3 sequences).

Germline	Framework 1	Kabat CDR 1	Framework 2	Kabat CDR 2	Framework 3
VH1-18*01 (SEQ ID NO: 183)	QVQLVQSGAEVKKPGASVKVSCKAS (SEQ ID NO: 215)	GYTFTSYGIS (SEQ ID NO: 216)	WVRQAPGQGLEWMG (SEQ ID NO: 217)	WISAYNGNTNYAQKLQG (SEQ ID NO: 218)	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR (SEQ ID NO: 219)
VH1-2*01 (SEQ ID NO: 184)	QVQLVQSGAEVKKPGASVKVSCKAS (SEQ ID NO: 215)	GYTFTGYYMH (SEQ ID NO: 220)	WVRQAPGQGLEWMG (SEQ ID NO: 217)	RINPNSGGTNYAQKFQG (SEQ ID NO: 221)	RVTSTRDTSISTAYMELSRLRSDDTVVYYCAR (SEQ ID NO: 222)
VH1-3*01 (SEQ ID NO: 185)	QVQLVQSGAEVKKPGASVKVSCKAS (SEQ ID NO: 215)	GYTFTSYAMH (SEQ ID NO: 223)	WVRQAPGQRLEWMG(SEQ ID NO: 224)	WINAGNGNTKYSQKFQG (SEQ ID NO: 225)	RVTITRDTSASTAYMELSSLRSEDTAVYYCAR(SEQ ID NO:

					226)
VH1-46*01 (SEQ ID NO: 186)	QVQLVQSGAEVKKPGASVKVSCKAS (SEQ ID NO: 215)	GYTFTSYYMH (SEQ ID NO: 227)	WVRQAPGQGLEWMG (SEQ ID NO: 217)	IINPSGGSTSYAQKFQG (SEQ ID NO: 228)	RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR (SEQ ID NO: 229)
VH1-69*01 (SEQ ID NO: 187)	QVQLVQSGAEVKKPGSSVKVSCKAS (SEQ ID NO: 230)	GGTFSSYAIS (SEQ ID NO: 231)	WVRQAPGQGLEWMG (SEQ ID NO: 217)	GIIPIFGTANYAQKFQG (SEQ ID NO: 232)	RVTITADESTSTAYMELSSLRSEDTAVYYCAR (SEQ ID NO: 233)
VH3-13*01 (SEQ ID NO: 188)	EVQLVESGGGLVQPGGSLRLSCAAS (SEQ ID NO: 234)	GFTFSSYDMH (SEQ ID NO: 235)	WVRQATGKGLEWVS (SEQ ID NO: 236)	AIGTAGDTYYPGSVKG (SEQ ID NO: 237)	RFTISRENAKNSLYLQMNSLRAGDTAVYYCAR (SEQ ID NO: 238)
VH3-20*01 (SEQ ID NO: 189)	EVQLVESGGGVVRPGGSLRLSCAAS (SEQ ID NO: 239)	GFTFDDYGMS (SEQ ID NO: 240)	WVRQAPGKGLEWVS (SEQ ID NO: 241)	GINWNGGSTGYADSVKG (SEQ ID NO: 242)	RFTISRDNAKNSLYLQMNSLRAEDTALYHCAR (SEQ ID NO: 243)
VH3-21*01 (SEQ ID NO: 190)	EVQLVESGGGLVKPGGSLRLSCAAS (SEQ ID NO: 244)	GFTFSSYSMN (SEQ ID NO: 245)	WVRQAPGKGLEWVS (SEQ ID NO: 241)	SISSSSSYIYYADSVKG (SEQ ID NO: 246)	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR (SEQ ID NO: 247)
VH3-23*01 (SEQ ID NO: 191)	EVQLLESGGGLVQPGGSLRLSCAAS (SEQ ID NO: 248)	GFTFSSYAMS (SEQ ID NO: 249)	WVRQAPGKGLEWVS (SEQ ID NO: 241)	AISGSGGSTYYADSVKG (SEQ ID NO: 250)	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK (SEQ ID NO: 251)
VH3-30*01 (SEQ ID NO: 192)	QVQLVESGGGVVQPGRSLRLSCAAS (SEQ ID NO: 252)	GFTFSSYAMH (SEQ ID NO: 253)	WVRQAPGKGLEWVA (SEQ ID NO: 254)	VISYDGSNKYYADSVKG (SEQ ID NO: 255)	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR (SEQ ID NO: 256)
VH3-33*01 (SEQ ID NO: 193)	QVQLVESGGGVVQPGRSLRLSCAAS (SEQ ID NO: 252)	GFTFSSYGMH (SEQ ID NO: 257)	WVRQAPGKGLEWVA (SEQ ID NO: 254)	VIWYDGSNKYYADSVKG (SEQ ID NO: 258)	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR (SEQ ID NO: 256)
VH3-66*01 (SEQ ID NO: 194)	EVQLVESGGGLVQPGGSLRLSCAAS (SEQ ID NO: 233)	GFTVSSNYMS (SEQ ID NO: 259)	WVRQAPGKGLEWVS (SEQ ID NO: 241)	VIYSGGSTYYADSVKG (SEQ ID NO: 260)	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR (SEQ ID NO: 256)
VH3-7*01 (SEQ ID NO: 195)	EVQLVESGGGLVQPGGSLRLSCAAS (SEQ ID NO: 233)	GFTFSSYWMS (SEQ ID NO: 261)	WVRQAPGKGLEWVA (SEQ ID NO: 254)	NIKQDGSEKYYVDSVKG (SEQ ID NO: 262)	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR (SEQ ID NO: 247)

VH3-9*01 (SEQ ID NO: 196)	EVQLVESGGGLVQPGRSLRLSCAAS (SEQ ID NO: 263)	GFTFDDYAMH (SEQ ID NO: 264)	WVRQAPGKGLEWVS (SEQ ID NO: 241)	GISWNSGSIGYADSVKG (SEQ ID NO: 265)	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK (SEQ ID NO: 266)
VH4-4*01 (SEQ ID NO: 197)	QVQLQESGPGLVKPPGTLSLTCAVS (SEQ ID NO: 267)	GGSISSSNWWS (SEQ ID NO: 268)	WVRQPPGKGLEWIG (SEQ ID NO: 269)	EIYHSGSTNYNPSLKS (SEQ ID NO: 270)	RVTISVDKSKNQFSLKLSSVTAADTAVYCCAR (SEQ ID NO: 271)
VH5-51*01 (SEQ ID NO: 198)	EVQLVQSGAEVKKPGESLKISCKGS (SEQ ID NO: 272)	GYSFTSYWIG (SEQ ID NO: 273)	WVRQMPGKGLEWMG (SEQ ID NO: 274)	IIYPGDSDTRYSPSFQG (SEQ ID NO: 275)	QVTISADKSISTAYLQWSSLKASDTAMYYCAR (SEQ ID NO: 276)
Vk1-12*01 (SEQ ID NO: 199)	DIQMTQSPSSVSASVGDRVTITC (SEQ ID NO: 277)	RASQGISSWLA (SEQ ID NO: 278)	WYQQKPGKAPKLLIY (SEQ ID NO: 279)	AASSLQS (SEQ ID NO: 280)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 281)
Vk1-27*01 (SEQ ID NO: 200)	DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 282)	RASQGISNYLA (SEQ ID NO: 283)	WYQQKPGKVPKLLIY (SEQ ID NO: 284)	AASTLQS (SEQ ID NO: 285)	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC (SEQ ID NO: 286)
Vk1-39*01 (SEQ ID NO: 201)	DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 282	RASQSISSYLN (SEQ ID NO: 287)	WYQQKPGKAPKLLIY (SEQ ID NO: 279)	AASSLQS (SEQ ID NO: 280)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 281)
Vk1D-16*01 (SEQ ID NO: 202)	DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 282	RASQGISSWLA (SEQ ID NO: 278)	WYQQKPEKAPKSLIY (SEQ ID NO: 288)	AASSLQS (SEQ ID NO: 280)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 281)
Vk2-28*01 (SEQ ID NO: 203)	DIVMTQSPLSLPVTPGEPASISC (SEQ ID NO: 289)	RSSQSLLHSNGYNYLD (SEQ ID NO: 290)	WYLQKPGQSPQLLIY (SEQ ID NO: 291)	LGSNRAS (SEQ ID NO: 292)	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC (SEQ ID NO: 293)
Vk3-11*01 (SEQ ID NO: 204)	EIVLTQSPATLSLSPGERATLSC (SEQ ID NO: 294)	RASQSVSSYLA (SEQ ID NO: 295)	WYQQKPGQAPRLLIY (SEQ ID NO: 296)	DASNRAT (SEQ ID NO: 297)	GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC (SEQ ID NO: 298)
Vk3-20*01 (SEQ ID NO: 205)	EIVLTQSPGTLSLSPGERATLSC (SEQ ID NO: 299)	RASQSVSSSYLA (SEQ ID NO: 300)	WYQQKPGQAPRLLIY (SEQ ID NO: 296)	GASSRAT (SEQ ID NO: 301)	GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC (SEQ ID NO: 302)
Vk3D-	EIVLTQSPATL	GASQSVSSSYL	WYQQKPGLAPR	DASSRAT	GIPDRFSGSGS

20*01 (SEQ ID NO: 206)	SLSPGERATLSC (SEQ ID NO: 294)	A (SEQ ID NO: 303)	LLIY (SEQ ID NO: 304)	(SEQ ID NO: 305)	GTDFTLTISRLEPEDFAVYYC (SEQ ID NO: 302)
Vl10-54*01 (SEQ ID NO: 207)	QAGLTQPPSVSKGLRQTATLTC (SEQ ID NO: 306)	TGNSNNVGNQGAA (SEQ ID NO: 307)	WLQQHQGHPPKLLSY (SEQ ID NO: 308)	RNNNRPS (SEQ ID NO: 309)	GISERLSASRSGNTASLTITGLQPEDEADYYC (SEQ ID NO: 310)
Vl1-40*01 (SEQ ID NO: 208)	QSVLTQPPSVSGAPGQRVTISC (SEQ ID NO: 311)	TGSSSNIGAGYDVH (SEQ ID NO: 312)	WYQQLPGTAPKLLIY (SEQ ID NO: 313)	GNSNRPS (SEQ ID NO: 314)	GVPDRFSGSKSGTSASLAITGLQAEDEADYYC (SEQ ID NO: 315)
Vl1-44*01 (SEQ ID NO: 209)	QSVLTQPPSASGTPGQRVTISC (SEQ ID NO: 316)	SGSSSNIGSNTVN (SEQ ID NO: 317)	WYQQLPGTAPKLLIY (SEQ ID NO: 313)	SNNQRPS (SEQ ID NO: 318)	GVPDRFSGSKSGTSASLAISGLQSEDEADYYC (SEQ ID NO: 319)
Vl2-14*01 (SEQ ID NO: 210)	QSALTQPASVSGSPGQSITISC (SEQ ID NO: 320)	TGTSSDVGGYNYVS (SEQ ID NO: 321)	WYQQHPGKAPKLMIY (SEQ ID NO: 322)	EVSNRPS (SEQ ID NO: 323)	GVSNRFSGSKSGNTASLTISGLQAEDEADYYC (SEQ ID NO: 324)
Vl3-19*01 (SEQ ID NO: 211)	SSELTQDPAVSVALGQTVRITC (SEQ ID NO: 325)	QGDSLRSYYAS (SEQ ID NO: 326)	WYQQKPGQAPVLVIY (SEQ ID NO: 327)	GKNNRPS (SEQ ID NO: 328)	GIPDRFSGSSSGNTASLTITGAQAEDEADYYC (SEQ ID NO: 329)
Vl3-9*01 (SEQ ID NO: 212)	SYELTQPLSVSVALGQTARITC (SEQ ID NO: 330)	GGNNIGSKNVH (SEQ ID NO: 331)	WYQQKPGQAPVLVIY (SEQ ID NO: 327)	RDSNRPS (SEQ ID NO: 332)	GIPERFSGSNSGNTATLTISRAQAGDEADYYC (SEQ ID NO: 333)
VH4-31*01 (SEQ ID NO: 213)	QVQLQESGPGLVKPSQTLSLTCTVS (SEQ ID NO: 334)	GGSISSGSYYWS (SEQ ID NO: 335)	WIRQHPGKGLEWIG (SEQ ID NO: 336)	YIYYSGSTYYNPSLKS (SEQ ID NO: 337)	RVTISVDTSKNQFSLKLSSVTAADTAVYY (SEQ ID NO: 338)

Table 5a. Sequences used to construct multispecific molecules.

Column 1: Construct	Column 2: heavy chain polypeptide 1 (HCP1)	Column 3: lambda light chain polypeptide (LLCP)	Column 4: heavy chain polypeptide 2 (HCP2)	Column 5: kappa light chain polypeptide (KLCP)
Multispecific molecule 1	SEQ ID NO: 178	SEQ ID NO: 145	SEQ ID NO: 179	SEQ ID NO: 118
Multispecific molecule 2	SEQ ID NO: 166	SEQ ID NO: 167	SEQ ID NO: 164	SEQ ID NO: 165

Multispecific molecule 3	SEQ ID NO: 170	SEQ ID NO: 163	SEQ ID NO: 168	SEQ ID NO: 106
Multispecific molecule 4	SEQ ID NO: 177	SEQ ID NO: 148	SEQ ID NO: 168	SEQ ID NO: 106
Multispecific molecule 5	SEQ ID NO: 180	SEQ ID NO: 136	SEQ ID NO: 168	SEQ ID NO: 106
Multispecific molecule 6	SEQ ID NO: 177	SEQ ID NO: 148	SEQ ID NO: 181	SEQ ID NO: 182
Multispecific molecule 7	SEQ ID NO: 166	SEQ ID NO: 167	SEQ ID NO: 181	SEQ ID NO: 182
Multispecific molecule 8	SEQ ID NO: 172	SEQ ID NO: 173	SEQ ID NO: 171	SEQ ID NO: 106
Multispecific molecule 9	SEQ ID NO: 170	SEQ ID NO: 173	SEQ ID NO: 168	SEQ ID NO: 106
Multispecific molecule 10	SEQ ID NO: 175	SEQ ID NO: 173	SEQ ID NO: 171	SEQ ID NO: 106
Multispecific molecule 11	SEQ ID NO: 174	SEQ ID NO: 173	SEQ ID NO: 168	SEQ ID NO: 106
Multispecific molecule 12	SEQ ID NO: 177	SEQ ID NO: 148	SEQ ID NO: 169	SEQ ID NO: 176

Table 5b. Corresponding germline sequences of multispecific molecules.

Column 1: Construct	Column 2: heavy chain polypeptide 1 (HCP1) corresponding germline sequence	Column 3: lambda light chain polypeptide (LLCP) corresponding germline sequence	Column 4: heavy chain polypeptide 2 (HCP2) corresponding germline sequence	Column 5: kappa light chain polypeptide (KLCP) corresponding germline sequence
Multispecific molecule 1	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)	VH3-23*01 (SEQ ID NO: 191)	Vk1-27*01 (SEQ ID NO: 200)
Multispecific molecule 2	VH3-66*01 (SEQ ID NO: 194)	Vl2-14*01 (SEQ ID NO: 210)	VH4-31*01 (SEQ ID NO: 213)	Vk1-39*01 (SEQ ID NO: 201)
Multispecific molecule 3	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)	VH3-30*01 (SEQ ID NO: 192)	Vk3-20*01 (SEQ ID NO: 205)
Multispecific molecule 4	Vk3-20*01 (SEQ ID NO: 205)	Vl3-19*01 (SEQ ID NO: 211)	VH3-30*01 (SEQ ID NO: 192)	Vk3-20*01 (SEQ ID NO: 205)
Multispecific molecule 5	VH1-69*01 (SEQ ID NO: 187)	Vl3-19*01 (SEQ ID NO: 211)	VH3-30*01 (SEQ ID NO: 192)	Vk3-20*01 (SEQ ID NO: 205)
Multispecific molecule 6	Vk3-20*01 (SEQ ID NO: 205)	Vl3-19*01 (SEQ ID NO: 211)	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)
Multispecific molecule 7	VH3-66*01 (SEQ ID NO: 194)	Vl2-14*01 (SEQ ID NO: 210)	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)
Multispecific molecule 8	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)	VH3-30*01 (SEQ ID NO: 192)	Vk3-20*01 (SEQ ID NO: 205)
Multispecific molecule 9	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)	VH3-30*01 (SEQ ID NO: 192)	Vk3-20*01 (SEQ ID NO: 205)
Multispecific molecule 10	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)	VH3-30*01 (SEQ ID NO: 192)	Vk3-20*01 (SEQ ID NO: 205)

Multispecific molecule 11	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)	VH3-30*01 (SEQ ID NO: 192)	Vk3-20*01 (SEQ ID NO: 205)
Multispecific molecule 12	Vk3-20*01 (SEQ ID NO: 205)	Vl3-19*01 (SEQ ID NO: 211)	VH3-30*01 (SEQ ID NO: 192)	Vk3-20*01 (SEQ ID NO: 205)

5. Kappa/Lambda select resin analysis of chain pairing.

The kappa and lambda light chain pairing of bispecific constructs was analyzed by incubating 1 mg of protein with 100 µL of either KappaSelect (GE 17-5458-01) or LambdaFabSelect (GE 17-5482-01) resin. After incubating for 1-3 hours, the resin was packed into a column, washed with 3 x 10 column volumes of Dulbecco's phosphate-buffered saline (DPBS, Life Technologies 14190-144). The bound protein was eluted from the column with 100 mM citrate, pH 2.46. The content of the load, flow-through, and elution fractions was analyzed using gels of samples reduced with 200 mM Bond-Breaker TCEP (Thermo Scientific 77720), allowing for the identification of the various chains. For quantitative assessment of the chain pairing, the amount of protein in the load and flow-through fractions was assessed using the absorbance at 280 nm with a NanoDrop.

The KappaSelect resin is an affinity resin that binds to the constant light chain of kappa antibodies. The elution from the KappaSelect will contain molecules with both a lambda and kappa light chain, where there are three possibilities (**FIGs. 1A**, **1B**, and **1D**). The LambdaFabSelect resin is an affinity resin that binds to the constant light chain of lambda antibodies. The elution from the LambdaFabSelect will contain molecules with both lambda and kappa light chain, where there are three possibilities (**FIGs. 1A**, **1C**, and **1D**).

6. Mass spectrometry for analysis of chain pairing.

To characterize the chain pairing in multispecific molecules, the purified samples were digested with immobilized papain (Thermo Scientific 20341) according to the manufacturer's instructions. Papain cleaves after the hinge region (**FIG. 2**), yielding two Fab arms. The digested molecules were run on a mass spectrometer, allowing identification of the two Fab arms based on the intact masses measured. The MS analysis allows for the discrimination of the different configurations (**FIG. 1A** vs. **FIG. 1D**), and the characterization of the extent of light-chain swapping.

Results

Example 1

NanoBiT based constructs were expressed by co-transfecting cells with DNA in a 1:1:1 heavy chain to light chain to competing light chain ratio. Table 3 shows individual combinations of a heavy chain (column 2), a light chain (column 3), and a competing light chain (column 4). Column 1 in Table 3 provides identifiers for each sequence combination. The molecules were purified and the luminescence assay was performed using the Nano-Glo reagent. The positive controls and negative controls are indicated. Positive controls represented 100% perfect pairing and the negative controls represented 50% perfect pairing. These values were used to quantify the pairing of the test constructs.

Table 6 shows the percent pairing for heavy chains and kappa light chains in the presence of competing lambda light chains (only the sequence combinations with a percent pairing of 75 % or greater were included). Table 7 shows the percent pairing for heavy chains and lambda light chains in the presence of competing kappa light chains (only the sequence combinations with a percent pairing of 75 % or greater were included). The identifiers shown in column 1 of Tables 6 and 7 correspond to the identifiers in column 1 of Table 3. In addition, Tables 6 and 7 also provide the corresponding germline sequences for the heavy chains (column 3), the light chains (column 4), and the competing light chains (column 5) used in each sequence combination.

Table 8a is a compilation of Tables 6 and 7 with samples that were successful in both directions. Each row of Table 8a shows a heavy chain/kappa light chain pair and a heavy chain/lambda light chain pair (indicated by the ID number), where the swapping of light chains between these two pairs is low based on the NanoBiT assay. Table 8b provides the corresponding germline sequences for the heavy chain/light chain pairs included in Table 8a. The identifiers shown in Tables 8a and 8b correspond to the identifiers in column 1 of Table 3.

Table 3. Sequences used to generate competition constructs.

Identifier for sequence combinations	Heavy chain	Light chain	Competing light chain
ID183 (positive control)	SEQ ID NO: 92	SEQ ID NO: 93	
ID184 (negative control)	SEQ ID NO: 92	SEQ ID NO: 93	SEQ ID NO: 94
ID185	SEQ ID NO: 92	SEQ ID NO: 93	SEQ ID NO: 136
ID186	SEQ ID NO: 92	SEQ ID NO: 93	SEQ ID NO: 139

ID187	SEQ ID NO: 92	SEQ ID NO: 93	SEQ ID NO: 142
ID188	SEQ ID NO: 92	SEQ ID NO: 93	SEQ ID NO: 145
ID189	SEQ ID NO: 92	SEQ ID NO: 93	SEQ ID NO: 148
ID190	SEQ ID NO: 92	SEQ ID NO: 93	SEQ ID NO: 151
ID191	SEQ ID NO: 92	SEQ ID NO: 93	SEQ ID NO: 154
ID192	SEQ ID NO: 92	SEQ ID NO: 93	SEQ ID NO: 157
ID193	SEQ ID NO: 92	SEQ ID NO: 93	SEQ ID NO: 160
ID194	SEQ ID NO: 92	SEQ ID NO: 93	SEQ ID NO: 163
ID195 (positive control)	SEQ ID NO: 95	SEQ ID NO: 96	
ID196 (negative control)	SEQ ID NO: 95	SEQ ID NO: 96	SEQ ID NO: 97
ID197	SEQ ID NO: 95	SEQ ID NO: 96	SEQ ID NO: 136
ID198	SEQ ID NO: 95	SEQ ID NO: 96	SEQ ID NO: 139
ID199	SEQ ID NO: 95	SEQ ID NO: 96	SEQ ID NO: 142
ID200	SEQ ID NO: 95	SEQ ID NO: 96	SEQ ID NO: 145
ID201	SEQ ID NO: 95	SEQ ID NO: 96	SEQ ID NO: 148
ID202	SEQ ID NO: 95	SEQ ID NO: 96	SEQ ID NO: 151
ID203	SEQ ID NO: 95	SEQ ID NO: 96	SEQ ID NO: 154
ID204	SEQ ID NO: 95	SEQ ID NO: 96	SEQ ID NO: 157
ID205	SEQ ID NO: 95	SEQ ID NO: 96	SEQ ID NO: 160
ID206	SEQ ID NO: 95	SEQ ID NO: 96	SEQ ID NO: 163
ID207 (positive control)	SEQ ID NO: 98	SEQ ID NO: 99	
ID208 (negative control)	SEQ ID NO: 98	SEQ ID NO: 99	SEQ ID NO: 100
ID209	SEQ ID NO: 98	SEQ ID NO: 99	SEQ ID NO: 136
ID210	SEQ ID NO: 98	SEQ ID NO: 99	SEQ ID NO: 139
ID211	SEQ ID NO: 98	SEQ ID NO: 99	SEQ ID NO: 142
ID212	SEQ ID NO: 98	SEQ ID NO: 99	SEQ ID NO: 145
ID213	SEQ ID NO: 98	SEQ ID NO: 99	SEQ ID NO: 148
ID214	SEQ ID NO: 98	SEQ ID NO: 99	SEQ ID NO: 151
ID215	SEQ ID NO: 98	SEQ ID NO: 99	SEQ ID NO: 154
ID216	SEQ ID NO: 98	SEQ ID NO: 99	SEQ ID NO: 157
ID217	SEQ ID NO: 98	SEQ ID NO: 99	SEQ ID NO: 160
ID218	SEQ ID NO: 98	SEQ ID NO: 99	SEQ ID NO: 163
ID219 (positive control)	SEQ ID NO: 101	SEQ ID NO: 102	
ID220 (negative control)	SEQ ID NO: 101	SEQ ID NO: 102	SEQ ID NO: 103
ID221	SEQ ID NO: 101	SEQ ID NO: 102	SEQ ID NO: 136
ID222	SEQ ID NO: 101	SEQ ID NO: 102	SEQ ID NO: 139
ID223	SEQ ID NO: 101	SEQ ID NO: 102	SEQ ID NO: 142
ID224	SEQ ID NO: 101	SEQ ID NO: 102	SEQ ID NO: 145
ID225	SEQ ID NO: 101	SEQ ID NO: 102	SEQ ID NO: 148
ID226	SEQ ID NO: 101	SEQ ID NO: 102	SEQ ID NO: 151
ID227	SEQ ID NO: 101	SEQ ID NO: 102	SEQ ID NO: 154
ID228	SEQ ID NO: 101	SEQ ID NO: 102	SEQ ID NO: 157
ID229	SEQ ID NO: 101	SEQ ID NO: 102	SEQ ID NO: 160
ID230	SEQ ID NO: 101	SEQ ID NO: 102	SEQ ID NO: 163
ID231 (positive control)	SEQ ID NO: 104	SEQ ID NO: 105	

ID232 (negative control)	SEQ ID NO: 104	SEQ ID NO: 105	SEQ ID NO: 106
ID233	SEQ ID NO: 104	SEQ ID NO: 105	SEQ ID NO: 136
ID234	SEQ ID NO: 104	SEQ ID NO: 105	SEQ ID NO: 139
ID235	SEQ ID NO: 104	SEQ ID NO: 105	SEQ ID NO: 142
ID236	SEQ ID NO: 104	SEQ ID NO: 105	SEQ ID NO: 145
ID237	SEQ ID NO: 104	SEQ ID NO: 105	SEQ ID NO: 148
ID238	SEQ ID NO: 104	SEQ ID NO: 105	SEQ ID NO: 151
ID239	SEQ ID NO: 104	SEQ ID NO: 105	SEQ ID NO: 154
ID240	SEQ ID NO: 104	SEQ ID NO: 105	SEQ ID NO: 157
ID241	SEQ ID NO: 104	SEQ ID NO: 105	SEQ ID NO: 160
ID242	SEQ ID NO: 104	SEQ ID NO: 105	SEQ ID NO: 163
ID243 (positive control)	SEQ ID NO: 107	SEQ ID NO: 108	
ID244 (negative control)	SEQ ID NO: 107	SEQ ID NO: 108	SEQ ID NO: 109
ID245	SEQ ID NO: 107	SEQ ID NO: 108	SEQ ID NO: 136
ID246	SEQ ID NO: 107	SEQ ID NO: 108	SEQ ID NO: 139
ID247	SEQ ID NO: 107	SEQ ID NO: 108	SEQ ID NO: 142
ID248	SEQ ID NO: 107	SEQ ID NO: 108	SEQ ID NO: 145
ID249	SEQ ID NO: 107	SEQ ID NO: 108	SEQ ID NO: 148
ID250	SEQ ID NO: 107	SEQ ID NO: 108	SEQ ID NO: 151
ID251	SEQ ID NO: 107	SEQ ID NO: 108	SEQ ID NO: 154
ID252	SEQ ID NO: 107	SEQ ID NO: 108	SEQ ID NO: 157
ID253	SEQ ID NO: 107	SEQ ID NO: 108	SEQ ID NO: 160
ID254	SEQ ID NO: 107	SEQ ID NO: 108	SEQ ID NO: 163
ID255 (positive control)	SEQ ID NO: 110	SEQ ID NO: 111	
ID256 (negative control)	SEQ ID NO: 110	SEQ ID NO: 111	SEQ ID NO: 112
ID257	SEQ ID NO: 110	SEQ ID NO: 111	SEQ ID NO: 136
ID258	SEQ ID NO: 110	SEQ ID NO: 111	SEQ ID NO: 139
ID259	SEQ ID NO: 110	SEQ ID NO: 111	SEQ ID NO: 142
ID260	SEQ ID NO: 110	SEQ ID NO: 111	SEQ ID NO: 145
ID261	SEQ ID NO: 110	SEQ ID NO: 111	SEQ ID NO: 148
ID262	SEQ ID NO: 110	SEQ ID NO: 111	SEQ ID NO: 151
ID263	SEQ ID NO: 110	SEQ ID NO: 111	SEQ ID NO: 154
ID264	SEQ ID NO: 110	SEQ ID NO: 111	SEQ ID NO: 157
ID265	SEQ ID NO: 110	SEQ ID NO: 111	SEQ ID NO: 160
ID266	SEQ ID NO: 110	SEQ ID NO: 111	SEQ ID NO: 163
ID267 (positive control)	SEQ ID NO: 113	SEQ ID NO: 114	
ID268 (negative control)	SEQ ID NO: 113	SEQ ID NO: 114	SEQ ID NO: 115
ID269	SEQ ID NO: 113	SEQ ID NO: 114	SEQ ID NO: 136
ID270	SEQ ID NO: 113	SEQ ID NO: 114	SEQ ID NO: 139
ID271	SEQ ID NO: 113	SEQ ID NO: 114	SEQ ID NO: 142
ID272	SEQ ID NO: 113	SEQ ID NO: 114	SEQ ID NO: 145
ID273	SEQ ID NO: 113	SEQ ID NO: 114	SEQ ID NO: 148
ID274	SEQ ID NO: 113	SEQ ID NO: 114	SEQ ID NO: 151
ID275	SEQ ID NO: 113	SEQ ID NO: 114	SEQ ID NO: 154
ID276	SEQ ID NO: 113	SEQ ID NO: 114	SEQ ID NO: 157

ID277	SEQ ID NO: 113	SEQ ID NO: 114	SEQ ID NO: 160
ID278	SEQ ID NO: 113	SEQ ID NO: 114	SEQ ID NO: 163
ID279 (positive control)	SEQ ID NO: 116	SEQ ID NO: 117	
ID280 (negative control)	SEQ ID NO: 116	SEQ ID NO: 117	SEQ ID NO: 118
ID281	SEQ ID NO: 116	SEQ ID NO: 117	SEQ ID NO: 136
ID282	SEQ ID NO: 116	SEQ ID NO: 117	SEQ ID NO: 139
ID283	SEQ ID NO: 116	SEQ ID NO: 117	SEQ ID NO: 142
ID284	SEQ ID NO: 116	SEQ ID NO: 117	SEQ ID NO: 145
ID285	SEQ ID NO: 116	SEQ ID NO: 117	SEQ ID NO: 148
ID286	SEQ ID NO: 116	SEQ ID NO: 117	SEQ ID NO: 151
ID287	SEQ ID NO: 116	SEQ ID NO: 117	SEQ ID NO: 154
ID288	SEQ ID NO: 116	SEQ ID NO: 117	SEQ ID NO: 157
ID289	SEQ ID NO: 116	SEQ ID NO: 117	SEQ ID NO: 160
ID290	SEQ ID NO: 116	SEQ ID NO: 117	SEQ ID NO: 163
ID291 (positive control)	SEQ ID NO: 119	SEQ ID NO: 120	
ID292 (negative control)	SEQ ID NO: 119	SEQ ID NO: 120	SEQ ID NO: 121
ID293	SEQ ID NO: 119	SEQ ID NO: 120	SEQ ID NO: 136
ID294	SEQ ID NO: 119	SEQ ID NO: 120	SEQ ID NO: 139
ID295	SEQ ID NO: 119	SEQ ID NO: 120	SEQ ID NO: 142
ID296	SEQ ID NO: 119	SEQ ID NO: 120	SEQ ID NO: 145
ID297	SEQ ID NO: 119	SEQ ID NO: 120	SEQ ID NO: 148
ID298	SEQ ID NO: 119	SEQ ID NO: 120	SEQ ID NO: 151
ID299	SEQ ID NO: 119	SEQ ID NO: 120	SEQ ID NO: 154
ID300	SEQ ID NO: 119	SEQ ID NO: 120	SEQ ID NO: 157
ID301	SEQ ID NO: 119	SEQ ID NO: 120	SEQ ID NO: 160
ID302	SEQ ID NO: 119	SEQ ID NO: 120	SEQ ID NO: 163
ID303 (positive control)	SEQ ID NO: 122	SEQ ID NO: 123	
ID304 (negative control)	SEQ ID NO: 122	SEQ ID NO: 123	SEQ ID NO: 124
ID305	SEQ ID NO: 122	SEQ ID NO: 123	SEQ ID NO: 136
ID306	SEQ ID NO: 122	SEQ ID NO: 123	SEQ ID NO: 139
ID307	SEQ ID NO: 122	SEQ ID NO: 123	SEQ ID NO: 142
ID308	SEQ ID NO: 122	SEQ ID NO: 123	SEQ ID NO: 145
ID309	SEQ ID NO: 122	SEQ ID NO: 123	SEQ ID NO: 148
ID310	SEQ ID NO: 122	SEQ ID NO: 123	SEQ ID NO: 151
ID311	SEQ ID NO: 122	SEQ ID NO: 123	SEQ ID NO: 154
ID312	SEQ ID NO: 122	SEQ ID NO: 123	SEQ ID NO: 157
ID313	SEQ ID NO: 122	SEQ ID NO: 123	SEQ ID NO: 160
ID314	SEQ ID NO: 122	SEQ ID NO: 123	SEQ ID NO: 163
ID315 (positive control)	SEQ ID NO: 125	SEQ ID NO: 126	
ID316 (negative control)	SEQ ID NO: 125	SEQ ID NO: 126	SEQ ID NO: 127
ID317	SEQ ID NO: 125	SEQ ID NO: 126	SEQ ID NO: 136
ID318	SEQ ID NO: 125	SEQ ID NO: 126	SEQ ID NO: 139
ID319	SEQ ID NO: 125	SEQ ID NO: 126	SEQ ID NO: 142
ID320	SEQ ID NO: 125	SEQ ID NO: 126	SEQ ID NO: 145
ID321	SEQ ID NO: 125	SEQ ID NO: 126	SEQ ID NO: 148

ID322	SEQ ID NO: 125	SEQ ID NO: 126	SEQ ID NO: 151
ID323	SEQ ID NO: 125	SEQ ID NO: 126	SEQ ID NO: 154
ID324	SEQ ID NO: 125	SEQ ID NO: 126	SEQ ID NO: 157
ID325	SEQ ID NO: 125	SEQ ID NO: 126	SEQ ID NO: 160
ID326	SEQ ID NO: 125	SEQ ID NO: 126	SEQ ID NO: 163
ID327 (positive control)	SEQ ID NO: 128	SEQ ID NO: 129	
ID328 (negative control)	SEQ ID NO: 128	SEQ ID NO: 129	SEQ ID NO: 130
ID329	SEQ ID NO: 128	SEQ ID NO: 129	SEQ ID NO: 136
ID330	SEQ ID NO: 128	SEQ ID NO: 129	SEQ ID NO: 139
ID331	SEQ ID NO: 128	SEQ ID NO: 129	SEQ ID NO: 142
ID332	SEQ ID NO: 128	SEQ ID NO: 129	SEQ ID NO: 145
ID333	SEQ ID NO: 128	SEQ ID NO: 129	SEQ ID NO: 148
ID334	SEQ ID NO: 128	SEQ ID NO: 129	SEQ ID NO: 151
ID335	SEQ ID NO: 128	SEQ ID NO: 129	SEQ ID NO: 154
ID336	SEQ ID NO: 128	SEQ ID NO: 129	SEQ ID NO: 157
ID337	SEQ ID NO: 128	SEQ ID NO: 129	SEQ ID NO: 160
ID338	SEQ ID NO: 128	SEQ ID NO: 129	SEQ ID NO: 163
ID339 (positive control)	SEQ ID NO: 131	SEQ ID NO: 132	
ID340 (negative control)	SEQ ID NO: 131	SEQ ID NO: 132	SEQ ID NO: 133
ID341	SEQ ID NO: 131	SEQ ID NO: 132	SEQ ID NO: 136
ID342	SEQ ID NO: 131	SEQ ID NO: 132	SEQ ID NO: 139
ID343	SEQ ID NO: 131	SEQ ID NO: 132	SEQ ID NO: 142
ID344	SEQ ID NO: 131	SEQ ID NO: 132	SEQ ID NO: 145
ID345	SEQ ID NO: 131	SEQ ID NO: 132	SEQ ID NO: 148
ID346	SEQ ID NO: 131	SEQ ID NO: 132	SEQ ID NO: 151
ID347	SEQ ID NO: 131	SEQ ID NO: 132	SEQ ID NO: 154
ID348	SEQ ID NO: 131	SEQ ID NO: 132	SEQ ID NO: 157
ID349	SEQ ID NO: 131	SEQ ID NO: 132	SEQ ID NO: 160
ID350	SEQ ID NO: 131	SEQ ID NO: 132	SEQ ID NO: 163
ID351 (positive control)	SEQ ID NO: 134	SEQ ID NO: 135	
ID352 (negative control)	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 136
ID353	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 94
ID354	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 97
ID355	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 100
ID356	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 103
ID357	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 106
ID358	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 109
ID359	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 112
ID360	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 115
ID361	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 118
ID362	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 121
ID363	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 124
ID364	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 127
ID365	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 130
ID366	SEQ ID NO: 134	SEQ ID NO: 135	SEQ ID NO: 133

ID367 (positive control)	SEQ ID NO: 137	SEQ ID NO: 138	
ID368 (negative control)	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 139
ID369	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 94
ID370	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 97
ID371	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 100
ID372	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 103
ID373	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 106
ID374	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 109
ID375	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 112
ID376	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 115
ID377	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 118
ID378	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 121
ID379	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 124
ID380	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 127
ID381	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 130
ID382	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 133
ID383 (positive control)	SEQ ID NO: 140	SEQ ID NO: 141	
ID384 (negative control)	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 142
ID385	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 94
ID386	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 97
ID387	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 100
ID388	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 103
ID389	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 106
ID390	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 109
ID391	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 112
ID392	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 115
ID393	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 118
ID394	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 121
ID395	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 124
ID396	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 127
ID397	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 130
ID398	SEQ ID NO: 140	SEQ ID NO: 141	SEQ ID NO: 133
ID399 (positive control)	SEQ ID NO: 143	SEQ ID NO: 144	
ID400 (negative control)	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 145
ID401	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 94
ID402	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 97
ID403	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 100
ID404	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 103
ID405	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 106
ID406	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 109
ID407	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 112
ID408	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 115
ID409	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 118
ID410	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 121
ID411	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 124

ID412	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 127
ID413	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 130
ID414	SEQ ID NO: 143	SEQ ID NO: 144	SEQ ID NO: 133
ID415 (positive control)	SEQ ID NO: 146	SEQ ID NO: 147	
ID416 (negative control)	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 148
ID417	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 94
ID418	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 97
ID419	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 100
ID420	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 103
ID421	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 106
ID422	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 109
ID423	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 112
ID424	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 115
ID425	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 118
ID426	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 121
ID427	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 124
ID428	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 127
ID429	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 130
ID430	SEQ ID NO: 146	SEQ ID NO: 147	SEQ ID NO: 133
ID431 (positive control)	SEQ ID NO: 149	SEQ ID NO: 150	
ID432 (negative control)	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 151
ID433	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 94
ID434	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 97
ID435	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 100
ID436	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 103
ID437	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 106
ID438	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 109
ID439	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 112
ID440	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 115
ID441	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 118
ID442	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 121
ID443	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 124
ID444	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 127
ID445	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 130
ID446	SEQ ID NO: 149	SEQ ID NO: 150	SEQ ID NO: 133
ID447 (positive control)	SEQ ID NO: 152	SEQ ID NO: 153	
ID448 (negative control)	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 154
ID449	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 94
ID450	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 97
ID451	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 100
ID452	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 103
ID453	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 106
ID454	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 109
ID455	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 112
ID456	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 115

ID457	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 118
ID458	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 121
ID459	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 124
ID460	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 127
ID461	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 130
ID462	SEQ ID NO: 152	SEQ ID NO: 153	SEQ ID NO: 133
ID463 (positive control)	SEQ ID NO: 155	SEQ ID NO: 156	
ID464 (negative control)	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 157
ID465	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 94
ID466	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 97
ID467	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 100
ID468	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 103
ID469	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 106
ID470	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 109
ID471	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 112
ID472	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 115
ID473	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 118
ID474	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 121
ID475	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 124
ID476	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 127
ID477	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 130
ID478	SEQ ID NO: 155	SEQ ID NO: 156	SEQ ID NO: 133
ID479 (positive control)	SEQ ID NO: 158	SEQ ID NO: 159	
ID480 (negative control)	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 160
ID481	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 94
ID482	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 97
ID483	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 100
ID484	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 103
ID485	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 106
ID486	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 109
ID487	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 112
ID488	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 115
ID489	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 118
ID490	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 121
ID491	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 124
ID492	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 127
ID493	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 130
ID494	SEQ ID NO: 158	SEQ ID NO: 159	SEQ ID NO: 133
ID495 (positive control)	SEQ ID NO: 161	SEQ ID NO: 162	
ID496 (negative control)	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 163
ID497	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 94
ID498	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 97
ID499	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 100
ID500	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 103
ID501	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 106

ID502	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 109
ID503	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 112
ID504	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 115
ID505	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 118
ID506	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 121
ID507	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 124
ID508	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 127
ID509	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 130
ID510	SEQ ID NO: 161	SEQ ID NO: 162	SEQ ID NO: 133

Table 6. Percent pairing for heavy chains and kappa light chains in the presence of competing lambda light chains as measured by the NanoBiT assay.

Column 1: Identifier for sequence combinations	Column 2: Percent pairing	Column 3: heavy chain polypeptide 2 (HCP2) corresponding germline	Column 4: kappa light chain polypeptide (KLCP) corresponding germline	Column 5: competing lambda light chain polypeptide (LLCP) corresponding germline
ID185	98	VH3-33*01 (SEQ ID NO: 193)	Vk1-39*01 (SEQ ID NO: 201)	Vl3-19*01 (SEQ ID NO: 211)
ID189	82	VH3-33*01 (SEQ ID NO: 193)	Vk1-39*01 (SEQ ID NO: 201)	Vl3-19*01 (SEQ ID NO: 211)
ID190	100	VH3-33*01 (SEQ ID NO: 193)	Vk1-39*01 (SEQ ID NO: 201)	Vl2-14*01 (SEQ ID NO: 210)
ID191	100	VH3-33*01 (SEQ ID NO: 193)	Vk1-39*01 (SEQ ID NO: 201)	Vl3-9*01 (SEQ ID NO: 212)
ID192	87	VH3-33*01 (SEQ ID NO: 193)	Vk1-39*01 (SEQ ID NO: 201)	Vl10-54*01 (SEQ ID NO: 207)
ID198	93	VH5-51*01 (SEQ ID NO: 198)	Vk3-20*01 (SEQ ID NO: 205)	Vl3-19*01 (SEQ ID NO: 211)
ID205	100	VH5-51*01 (SEQ ID NO: 198)	Vk3-20*01 (SEQ ID NO: 205)	Vl10-54*01 (SEQ ID NO: 207)
ID206	93	VH5-51*01 (SEQ ID NO: 198)	Vk3-20*01 (SEQ ID NO: 205)	Vl1-44*01 (SEQ ID NO: 209)
ID209	95	VH3-13*01 (SEQ ID NO: 188)	Vk1D-16*01 (SEQ ID NO: 202)	Vl3-19*01 (SEQ ID NO: 211)
ID211	93	VH3-13*01 (SEQ ID NO: 188)	Vk1D-16*01 (SEQ ID NO: 202)	Vl1-40*01 (SEQ ID NO: 208)
ID213	90	VH3-13*01 (SEQ ID NO: 188)	Vk1D-16*01 (SEQ ID NO: 202)	Vl3-19*01 (SEQ ID NO: 211)
ID214	100	VH3-13*01 (SEQ ID NO: 188)	Vk1D-16*01 (SEQ ID NO: 202)	Vl2-14*01 (SEQ ID NO: 210)
ID215	95	VH3-13*01 (SEQ ID NO: 188)	Vk1D-16*01 (SEQ ID NO: 202)	Vl3-9*01 (SEQ ID NO: 212)
ID216	96	VH3-13*01 (SEQ ID NO: 188)	Vk1D-16*01 (SEQ ID NO: 202)	Vl10-54*01 (SEQ ID NO: 207)

ID217	100	VH3-13*01 (SEQ ID NO: 188)	Vk1D-16*01 (SEQ ID NO: 202)	Vl10-54*01 (SEQ ID NO: 207)
ID218	100	VH3-13*01 (SEQ ID NO: 188)	Vk1D-16*01 (SEQ ID NO: 202)	Vl1-44*01 (SEQ ID NO: 209)
ID222	100	VH1-3*01 (SEQ ID NO: 185)	Vk3D-20*01 (SEQ ID NO: 206)	Vl3-19*01 (SEQ ID NO: 211)
ID229	98	VH1-3*01 (SEQ ID NO: 185)	Vk3D-20*01 (SEQ ID NO: 206)	Vl10-54*01 (SEQ ID NO: 207)
ID230	83	VH1-3*01 (SEQ ID NO: 185)	Vk3D-20*01 (SEQ ID NO: 206)	Vl1-44*01 (SEQ ID NO: 209)
ID228	93	VH1-3*01 (SEQ ID NO: 185)	Vk3D-20*01 (SEQ ID NO: 206)	Vl10-54*01 (SEQ ID NO: 207)
ID235	90	VH3-30*01 (SEQ ID NO: 192)	Vk3-20*01 (SEQ ID NO: 205)	Vl1-40*01 (SEQ ID NO: 208)
ID236	100	VH3-30*01 (SEQ ID NO: 192)	Vk3-20*01 (SEQ ID NO: 205)	Vl3-19*01 (SEQ ID NO: 211)
ID242	100	VH3-30*01 (SEQ ID NO: 192)	Vk3-20*01 (SEQ ID NO: 205)	Vl1-44*01 (SEQ ID NO: 209)
ID241	100	VH3-30*01 (SEQ ID NO: 192)	Vk3-20*01 (SEQ ID NO: 205)	Vl10-54*01 (SEQ ID NO: 207)
ID259	75	VH1-18*01 (SEQ ID NO: 183)	Vk3-20*01 (SEQ ID NO: 205)	Vl1-40*01 (SEQ ID NO: 208)
ID262	90	VH1-18*01 (SEQ ID NO: 183)	Vk3-20*01 (SEQ ID NO: 205)	Vl2-14*01 (SEQ ID NO: 210)
ID288	95	VH3-23*01 (SEQ ID NO: 191)	Vk1-27*01 (SEQ ID NO: 200)	Vl10-54*01 (SEQ ID NO: 207)
ID289	100	VH3-23*01 (SEQ ID NO: 191)	Vk1-27*01 (SEQ ID NO: 200)	Vl10-54*01 (SEQ ID NO: 207)
ID284	84	VH3-23*01 (SEQ ID NO: 191)	Vk1-27*01 (SEQ ID NO: 200)	Vl3-19*01 (SEQ ID NO: 211)
ID286	81	VH3-23*01 (SEQ ID NO: 191)	Vk1-27*01 (SEQ ID NO: 200)	Vl2-14*01 (SEQ ID NO: 210)
ID290	96	VH3-23*01 (SEQ ID NO: 191)	Vk1-27*01 (SEQ ID NO: 200)	Vl1-44*01 (SEQ ID NO: 209)
ID295	95	VH3-21*01 (SEQ ID NO: 190)	Vk3-20*01 (SEQ ID NO: 205)	Vl1-40*01 (SEQ ID NO: 208)
ID299	99	VH3-21*01 (SEQ ID NO: 190)	Vk3-20*01 (SEQ ID NO: 205)	Vl3-9*01 (SEQ ID NO: 212)
ID302	100	VH3-21*01 (SEQ ID NO: 190)	Vk3-20*01 (SEQ ID NO: 205)	Vl1-44*01 (SEQ ID NO: 209)
ID301	100	VH3-21*01 (SEQ ID NO: 190)	Vk3-20*01 (SEQ ID NO: 205)	Vl10-54*01 (SEQ ID NO: 207)
ID306	94	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)	Vl3-19*01 (SEQ ID NO: 211)
ID307	98	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)	Vl1-40*01 (SEQ ID NO: 208)

ID308	100	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)	Vl3-19*01 (SEQ ID NO: 211)
ID309	93	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)	Vl3-19*01 (SEQ ID NO: 211)
ID310	94	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)	Vl2-14*01 (SEQ ID NO: 210)
ID312	88	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)	Vl10-54*01 (SEQ ID NO: 207)
ID313	100	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)	Vl10-54*01 (SEQ ID NO: 207)
ID314	100	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)	Vl1-44*01 (SEQ ID NO: 209)
ID317	100	VH3-9*01 (SEQ ID NO: 196)	Vk1-12*01 (SEQ ID NO: 199)	Vl3-19*01 (SEQ ID NO: 211)
ID318	99	VH3-9*01 (SEQ ID NO: 196)	Vk1-12*01 (SEQ ID NO: 199)	Vl3-19*01 (SEQ ID NO: 211)
ID320	100	VH3-9*01 (SEQ ID NO: 196)	Vk1-12*01 (SEQ ID NO: 199)	Vl3-19*01 (SEQ ID NO: 211)
ID324	100	VH3-9*01 (SEQ ID NO: 196)	Vk1-12*01 (SEQ ID NO: 199)	Vl10-54*01 (SEQ ID NO: 207)
ID323	84	VH3-9*01 (SEQ ID NO: 196)	Vk1-12*01 (SEQ ID NO: 199)	Vl3-9*01 (SEQ ID NO: 212)
ID246	100	VH5-51*01 (SEQ ID NO: 198)	Vk3-20*01 (SEQ ID NO: 205)	Vl3-19*01 (SEQ ID NO: 211)
ID253	80	VH5-51*01 (SEQ ID NO: 198)	Vk3-20*01 (SEQ ID NO: 205)	Vl10-54*01 (SEQ ID NO: 207)
ID254	100	VH5-51*01 (SEQ ID NO: 198)	Vk3-20*01 (SEQ ID NO: 205)	Vl1-44*01 (SEQ ID NO: 209)
ID274	79	VH4-4*01 (SEQ ID NO: 197)	Vk2-28*01 (SEQ ID NO: 203)	Vl2-14*01 (SEQ ID NO: 210)
ID278	79	VH4-4*01 (SEQ ID NO: 197)	Vk2-28*01 (SEQ ID NO: 203)	Vl1-44*01 (SEQ ID NO: 209)
ID336	76	VH3-23*01 (SEQ ID NO: 191)	Vk3-11*01 (SEQ ID NO: 204)	Vl10-54*01 (SEQ ID NO: 207)
ID341	100	VH3-66*01 (SEQ ID NO: 194)	Vk1-39*01 (SEQ ID NO: 201)	Vl3-19*01 (SEQ ID NO: 211)
ID349	100	VH3-66*01 (SEQ ID NO: 194)	Vk1-39*01 (SEQ ID NO: 201)	Vl10-54*01 (SEQ ID NO: 207)
ID344	100	VH3-66*01 (SEQ ID NO: 194)	Vk1-39*01 (SEQ ID NO: 201)	Vl3-19*01 (SEQ ID NO: 211)
ID342	100	VH3-66*01 (SEQ ID NO: 194)	Vk1-39*01 (SEQ ID NO: 201)	Vl3-19*01 (SEQ ID NO: 211)
ID343	84	VH3-66*01 (SEQ ID NO: 194)	Vk1-39*01 (SEQ ID NO: 201)	Vl1-40*01 (SEQ ID NO: 208)
ID347	100	VH3-66*01 (SEQ ID NO: 194)	Vk1-39*01 (SEQ ID NO: 201)	Vl3-9*01 (SEQ ID NO: 212)

ID348	100	VH3-66*01 (SEQ ID NO: 194)	Vk1-39*01 (SEQ ID NO: 201)	Vl10-54*01 (SEQ ID NO: 207)
ID350	100	VH3-66*01 (SEQ ID NO: 194)	Vk1-39*01 (SEQ ID NO: 201)	Vl1-44*01 (SEQ ID NO: 209)

Table 7. Percent pairing for heavy chains and lambda light chains in the presence of competing kappa light chains as measured by the NanoBiT assay.

Column 1: Identifier for sequence combinations	Column 2: Percent pairing	Column 3: heavy chain polypeptide 1 (HCP1) corresponding germline	Column 4: lambda light chain polypeptide (LLCP) corresponding germline	Column 5: Competing kappa light chain polypeptide (KLCP) corresponding germline
ID357	96	VH1-69*01 (SEQ ID NO: 187)	Vl3-19*01 (SEQ ID NO: 211)	Vk3-20*01 (SEQ ID NO: 205)
ID359	95	VH1-69*01 (SEQ ID NO: 187)	Vl3-19*01 (SEQ ID NO: 211)	Vk3-20*01 (SEQ ID NO: 205)
ID363	100	VH1-69*01 (SEQ ID NO: 187)	Vl3-19*01 (SEQ ID NO: 211)	Vk3-11*01 (SEQ ID NO: 204)
ID366	100	VH1-69*01 (SEQ ID NO: 187)	Vl3-19*01 (SEQ ID NO: 211)	Vk1-39*01 (SEQ ID NO: 201)
ID378	94	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)	Vk3-20*01 (SEQ ID NO: 205)
ID379	100	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)	Vk3-11*01 (SEQ ID NO: 204)
ID372	100	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)	Vk3D-20*01 (SEQ ID NO: 206)
ID374	100	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)	Vk3-20*01 (SEQ ID NO: 205)
ID380	95	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)	Vk1-12*01 (SEQ ID NO: 199)
ID386	96	VH5-51*01 (SEQ ID NO: 198)	Vl1-40*01 (SEQ ID NO: 208)	Vk3-20*01 (SEQ ID NO: 205)
ID392	93	VH5-51*01 (SEQ ID NO: 198)	Vl1-40*01 (SEQ ID NO: 208)	Vk2-28*01 (SEQ ID NO: 203)
ID393	91	VH5-51*01 (SEQ ID NO: 198)	Vl1-40*01 (SEQ ID NO: 208)	Vk1-27*01 (SEQ ID NO: 200)
ID395	100	VH5-51*01 (SEQ ID NO: 198)	Vl1-40*01 (SEQ ID NO: 208)	Vk3-11*01 (SEQ ID NO: 204)
ID462	79	VH1-69*01 (SEQ ID NO: 187)	Vl3-9*01 (SEQ ID NO: 212)	Vk1-39*01 (SEQ ID NO: 201)
ID472	90	VH1-2*01 (SEQ ID NO: 184)	Vl10-54*01 (SEQ ID NO: 207)	Vk2-28*01 (SEQ ID NO: 203)
ID475	80	VH1-2*01 (SEQ ID NO: 184)	Vl10-54*01 (SEQ ID NO: 207)	Vk3-11*01 (SEQ ID NO: 204)
ID476	77	VH1-2*01 (SEQ ID	Vl10-54*01 (SEQ ID	Vk1-12*01 (SEQ ID

		NO: 184)	NO: 207)	NO: 199)
ID477	100	VH1-2*01 (SEQ ID NO: 184)	Vl10-54*01 (SEQ ID NO: 207)	Vk3-11*01 (SEQ ID NO: 204)
ID478	100	VH1-2*01 (SEQ ID NO: 184)	Vl10-54*01 (SEQ ID NO: 207)	Vk1-39*01 (SEQ ID NO: 201)
ID481	100	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)	Vk1-39*01 (SEQ ID NO: 201)
ID482	89	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)	Vk3-20*01 (SEQ ID NO: 205)
ID483	99	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)	Vk1D-16*01 (SEQ ID NO: 202)
ID484	100	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)	Vk3D-20*01 (SEQ ID NO: 206)
ID485	98	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)	Vk3-20*01 (SEQ ID NO: 205)
ID486	95	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)	Vk3-20*01 (SEQ ID NO: 205)
ID488	97	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)	Vk2-28*01 (SEQ ID NO: 203)
ID493	99	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)	Vk3-11*01 (SEQ ID NO: 204)
ID494	99	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)	Vk1-39*01 (SEQ ID NO: 201)
ID402	100	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)	Vk3-20*01 (SEQ ID NO: 205)
ID404	80	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)	Vk3D-20*01 (SEQ ID NO: 206)
ID405	93	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)	Vk3-20*01 (SEQ ID NO: 205)
ID407	100	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)	Vk3-20*01 (SEQ ID NO: 205)
ID408	86	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)	Vk2-28*01 (SEQ ID NO: 203)
ID409	90	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)	Vk1-27*01 (SEQ ID NO: 200)
ID411	100	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)	Vk3-11*01 (SEQ ID NO: 204)
ID412	100	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)	Vk1-12*01 (SEQ ID NO: 199)
ID414	100	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)	Vk1-39*01 (SEQ ID NO: 201)
ID418	100	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)	Vk3-20*01 (SEQ ID NO: 205)
ID420	84	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)	Vk3D-20*01 (SEQ ID NO: 206)
ID421	77	VH3-20*01 (SEQ ID	Vl3-19*01 (SEQ ID	Vk3-20*01 (SEQ ID

		NO: 189)	NO: 211)	NO: 205)
ID422	100	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)	Vk3-20*01 (SEQ ID NO: 205)
ID423	100	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)	Vk3-20*01 (SEQ ID NO: 205)
ID424	81	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)	Vk2-28*01 (SEQ ID NO: 203)
ID430	100	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)	Vk1-39*01 (SEQ ID NO: 201)
ID434	90	VH1-46*01 (SEQ ID NO: 186)	Vl2-14*01 (SEQ ID NO: 210)	Vk3-20*01 (SEQ ID NO: 205)
ID435	90	VH1-46*01 (SEQ ID NO: 186)	Vl2-14*01 (SEQ ID NO: 210)	Vk1D-16*01 (SEQ ID NO: 202)
ID436	81	VH1-46*01 (SEQ ID NO: 186)	Vl2-14*01 (SEQ ID NO: 210)	Vk3D-20*01 (SEQ ID NO: 206)
ID440	75	VH1-46*01 (SEQ ID NO: 186)	Vl2-14*01 (SEQ ID NO: 210)	Vk2-28*01 (SEQ ID NO: 203)
ID441	79	VH1-46*01 (SEQ ID NO: 186)	Vl2-14*01 (SEQ ID NO: 210)	Vk1-27*01 (SEQ ID NO: 200)
ID443	100	VH1-46*01 (SEQ ID NO: 186)	Vl2-14*01 (SEQ ID NO: 210)	Vk3-11*01 (SEQ ID NO: 204)
ID446	87	VH1-46*01 (SEQ ID NO: 186)	Vl2-14*01 (SEQ ID NO: 210)	Vk1-39*01 (SEQ ID NO: 201)
ID498	100	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)	Vk3-20*01 (SEQ ID NO: 205)
ID499	100	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)	Vk1D-16*01 (SEQ ID NO: 202)
ID500	100	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)	Vk3D-20*01 (SEQ ID NO: 206)
ID501	100	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)	Vk3-20*01 (SEQ ID NO: 205)
ID502	80	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)	Vk3-20*01 (SEQ ID NO: 205)
ID506	100	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)	Vk3-20*01 (SEQ ID NO: 205)

Table 8a. Two-way pairs based on NanoBiT data.

Identifier for sequence combinations	Percent pairing	Identifier for sequence combinations	Percent pairing
ID205	100	ID482	89
ID206	93	ID498	100
ID214	100	ID435	90
ID217	100	ID483	99
ID218	100	ID499	100

ID222	100	ID372	100
ID229	98	ID484	100
ID230	83	ID500	100
ID236	100	ID405	93
ID242	100	ID501	100
ID241	100	ID485	98
ID259	75	ID392	93
ID284	84	ID409	90
ID286	81	ID441	79
ID302	100	ID506	100
ID306	94	ID379	100
ID307	98	ID395	100
ID308	100	ID411	100
ID310	94	ID443	100
ID312	88	ID475	80
ID318	99	ID380	95
ID320	100	ID412	100
ID324	100	ID476	77
ID246	100	ID374	100
ID253	80	ID486	95
ID254	100	ID502	80
ID274	79	ID440	75
ID336	76	ID477	100
ID341	100	ID366	100
ID349	100	ID494	99
ID344	100	ID414	100
ID347	100	ID462	79
ID348	100	ID478	100

Table 8b. Corresponding germline sequences of two-way pairs based on NanoBiT data

Column 1: Identifier for sequence combinations	Column 2: heavy chain polypeptide 1 (HCP1) corresponding germline	Column 3: lambda light chain polypeptide (LLCP) corresponding germline	Column 4: Identifier for sequence combinations	Column 5: heavy chain polypeptide 2 (HCP2) corresponding germline	Column 6: kappa light chain polypeptide (KLCP) corresponding germline
ID205	VH5-51*01 (SEQ ID NO: 198)	VK3-20*01 (SEQ ID NO: 205)	ID482	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)
ID206	VH5-51*01 (SEQ ID NO: 198)	VK3-20*01 (SEQ ID NO: 205)	ID498	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)
ID214	VH3-13*01 (SEQ ID NO: 188)	VK1D-16*01 (SEQ ID NO: 202)	ID435	VH1-46*01 (SEQ ID NO: 186)	Vl2-14*01 (SEQ ID NO: 210)

ID217	VH3-13*01 (SEQ ID NO: 188)	VK1D-16*01 (SEQ ID NO: 202)	ID483	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)
ID218	VH3-13*01 (SEQ ID NO: 188)	VK1D-16*01 (SEQ ID NO: 202)	ID499	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)
ID222	VH1-3*01 (SEQ ID NO: 185)	VK3D-20*01 (SEQ ID NO: 206)	ID372	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)
ID229	VH1-3*01 (SEQ ID NO: 185)	VK3D-20*01 (SEQ ID NO: 206)	ID484	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)
ID230	VH1-3*01 (SEQ ID NO: 185)	VK3D-20*01 (SEQ ID NO: 206)	ID500	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)
ID236	VH3-30*01 (SEQ ID NO: 192)	VK3-20*01 (SEQ ID NO: 205)	ID405	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)
ID242	VH3-30*01 (SEQ ID NO: 192)	VK3-20*01 (SEQ ID NO: 205)	ID501	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)
ID241	VH3-30*01 (SEQ ID NO: 192)	VK3-20*01 (SEQ ID NO: 205)	ID485	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)
ID259	VH1-18*01 (SEQ ID NO: 183)	VK3-20*01 (SEQ ID NO: 205)	ID392	VH5-51*01 (SEQ ID NO: 198)	Vl1-40*01 (SEQ ID NO: 208)
ID284	VH3-23*01 (SEQ ID NO: 191)	VK1-27*01 (SEQ ID NO: 200)	ID409	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)
ID286	VH3-23*01 (SEQ ID NO: 191)	VK1-27*01 (SEQ ID NO: 200)	ID441	VH1-46*01 (SEQ ID NO: 186)	Vl2-14*01 (SEQ ID NO: 210)
ID302	VH3-21*01 (SEQ ID NO: 190)	VK3-20*01 (SEQ ID NO: 205)	ID506	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)
ID306	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)	ID379	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)
ID307	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)	ID395	VH5-51*01 (SEQ ID NO: 198)	Vl1-40*01 (SEQ ID NO: 208)
ID308	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)	ID411	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)
ID310	VH3-33*01 (SEQ ID NO: 193)	Vk3-11*01 (SEQ ID NO: 204)	ID443	VH1-46*01 (SEQ ID NO: 186)	Vl2-14*01 (SEQ ID NO: 210)
ID312	VH3-33*01 (SEQ ID NO:	Vk3-11*01 (SEQ ID NO:	ID475	VH1-2*01 (SEQ ID NO:	Vl10-54*01 (SEQ ID NO:

	193)	204)		184)	207)
ID318	VH3-9*01 (SEQ ID NO: 196)	Vk1-12*01 (SEQ ID NO: 199)	ID380	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)
ID320	VH3-9*01 (SEQ ID NO: 196)	Vk1-12*01 (SEQ ID NO: 199)	ID412	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)
ID324	VH3-9*01 (SEQ ID NO: 196)	Vk1-12*01 (SEQ ID NO: 199)	ID476	VH1-2*01 (SEQ ID NO: 184)	Vl10-54*01 (SEQ ID NO: 207)
ID246	VH5-51*01 (SEQ ID NO: 198)	VK3-20*01 (SEQ ID NO: 205)	ID374	VH3-20*01 (SEQ ID NO: 189)	Vl3-19*01 (SEQ ID NO: 211)
ID253	VH5-51*01 (SEQ ID NO: 198)	VK3-20*01 (SEQ ID NO: 205)	ID486	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)
ID254	VH5-51*01 (SEQ ID NO: 198)	VK3-20*01 (SEQ ID NO: 205)	ID502	VH3-33*01 (SEQ ID NO: 193)	Vl1-44*01 (SEQ ID NO: 209)
ID274	VH4-4*01 (SEQ ID NO: 197)	VK2-28*01 (SEQ ID NO: 203)	ID440	VH1-46*01 (SEQ ID NO: 186)	Vl2-14*01 (SEQ ID NO: 210)
ID336	VH3-23*01 (SEQ ID NO: 191)	Vk3-11*01 (SEQ ID NO: 204)	ID477	VH1-2*01 (SEQ ID NO: 184)	Vl10-54*01 (SEQ ID NO: 207)
ID341	VH3-66*01 (SEQ ID NO: 194)	Vk1-39*01 (SEQ ID NO: 201)	ID366	VH1-69*01 (SEQ ID NO: 187)	Vl3-19*01 (SEQ ID NO: 211)
ID349	VH3-66*01 (SEQ ID NO: 194)	Vk1-39*01 (SEQ ID NO: 201)	ID494	VH3-7*01 (SEQ ID NO: 195)	Vl10-54*01 (SEQ ID NO: 207)
ID344	VH3-66*01 (SEQ ID NO: 194)	Vk1-39*01 (SEQ ID NO: 201)	ID414	VH3-9*01 (SEQ ID NO: 196)	Vl3-19*01 (SEQ ID NO: 211)
ID347	VH3-66*01 (SEQ ID NO: 194)	Vk1-39*01 (SEQ ID NO: 201)	ID462	VH1-69*01 (SEQ ID NO: 187)	Vl3-9*01 (SEQ ID NO: 212)
ID348	VH3-66*01 (SEQ ID NO: 194)	Vk1-39*01 (SEQ ID NO: 201)	ID478	VH1-2*01 (SEQ ID NO: 184)	Vl10-54*01 (SEQ ID NO: 207)

Example 2

Multispecific molecule 1 comprises an α-IGF1R arm and an α-HER3 arm. The α-IGF1R arm comprises a first chain of the amino acid sequence of SEQ ID NO: 179 and a second chain of the amino acid sequence of SEQ ID NO: 118. The α-HER3 arm comprises a first chain of the

amino acid sequence of SEQ ID NO: 178 and a second chain of the amino acid sequence of SEQ ID NO: 145. The configuration of multispecific molecule 1 is shown in FIG. 5.

Multispecific molecule 1 was expressed by co-transfecting cells with expression vectors comprising polynucleotide sequences of SEQ ID NO: 86, SEQ ID NO: 54, SEQ ID NO: 87, and SEQ ID NO: 27. Multispecific molecule 1 was purified and a SDS-PAGE gel of the final product is shown in FIG. 11. FIG. 19 shows the size exclusion chromatogram of multispecific molecule 1. A KappaSelect and LambdaFabSelect analysis was performed with multispecific molecule 1, shown in FIG. 24. The gel shows a small amount of protein in the flow-through from the KappaSelect and LambdaFab columns. The quantitative results of this analysis are shown in Table 9, giving 85% fidelity for the kappa chain and 85% fidelity for the lambda chain. These results correlate with the NanoBiT data of ID284 and ID409, which have the same Fab arms, with 84 % and 90 % fidelity, respectively.

Table 9. Results of quantitative kappa/lambda select analysis.

Construct	Percent pairing from KappaSelect column	Percent pairing from LambdaFabSelect
Multispecific molecule 1	85	85
Multispecific molecule 2	88	86

Example 3

Multispecific molecule 2 comprises an α-mesothelin arm and an α-PDL1 arm. The an α-mesothelin arm comprises a first chain of the amino acid sequence of SEQ ID NO: 164 and a second chain of the amino acid sequence of SEQ ID NO: 165. The α-PDL1 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 166 and a second chain of the amino acid sequence of SEQ ID NO: 167. The configuration of multispecific molecule 2 is shown in FIG. 5.

Multispecific molecule 2 was expressed by co-transfecting cells with expression vectors comprising polynucleotide sequences of SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, and SEQ ID NO: 85. A KappaSelect and LambdaFabSelect analysis was performed with multispecific molecule 2, shown in FIG. 23. The gel shows a small amount of protein in the flow-through from the KappaSelect and LambdaFab columns. The quantitative results of this analysis are shown in Table 9. The fidelity for the KappaSelect column is 88 % and the fidelity for the LambdaFabSelect column is 86 %.

Example 4

Multispecific molecule 3 comprises an α-CTLA4 arm and an α-IL12β arm. The α-CTLA4 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 168 and a second chain of the amino acid sequence of SEQ ID NO: 106. The α-IL12β arm comprises a first chain of the amino acid sequence of SEQ ID NO: 170 and a second chain of the amino acid sequence of SEQ ID NO: 163. The configuration of multispecific molecule 3 is shown in FIG. 5.

Multispecific molecule 3 was expressed by co-transfecting cells with expression vectors comprising polynucleotide sequences of SEQ ID NO: 78, SEQ ID NO: 15, SEQ ID NO: 91, and SEQ ID NO: 72. Multispecific molecule 3 was purified and a SDS-PAGE gel of the final product is shown in FIG. 12. FIG. 20. shows the size exclusion chromatogram of multispecific molecule 3. A KappaSelect and LambdaFabSelect analysis was performed with multispecific molecule 3, shown in FIG. 25. The gel shows no protein in the flow-through of the KappaSelect or LambdaFabSelect columns, suggesting correct light chain pairing. The mass spectrometry data of the papain cleavage of multispecific molecule 3 is shown in FIG. 31 and summarized in Table 10. This data only shows correctly paired Fabs, further illustrating that there is no mispairing for these kappa and lambda chains. These results also correlate with the NanoBiT data of ID242 and ID501, which have the same Fab arms, and both showed 100 % chain fidelity.

Table 10. Mass spectrometry results for multispecific molecule 3.

Fab Pairing	Predicted Mass (Da)	Observed Mass (Da)
Kappa heavy chain/kappa light chain	47652.9	47634.9
Kappa heavy chain/lambda light chain	47390.4	N/A
Lambda heavy chain/lambda light chain	46974.6	46940.4
Lambda heavy chain/kappa light chain	47237.2	N/A

Example 5

Multispecific molecule 4 comprises an α-CTLA4 arm and an α-TRAILR2 arm. The α-CTLA4 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 168 and a second chain of the amino acid sequence of SEQ ID NO: 106. The α-TRAILR2 arm comprises a first

chain of the amino acid sequence of SEQ ID NO: 177 and a second chain of the amino acid sequence of SEQ ID NO: 148. The configuration of multispecific molecule 4 is shown in FIG. 5.

Multispecific molecule 4 was expressed by co-transfecting cells with expression vectors comprising polynucleotide sequences of SEQ ID NO: 78, SEQ ID NO: 15, SEQ ID NO: 81, and SEQ ID NO: 57. Multispecific molecule 4 was purified and a SDS-PAGE gel of the final product is shown in FIG. 13. The mass spectrometry data of the papain cleavage of multispecific molecule 4 is shown in FIG. 31 and summarized in Table 11. This data shows one incorrect Fab pairing where the kappa heavy chain is paired with the lambda light chain. This correlates with the NanoBiT data of ID237 and ID421, which have the same Fab arms as multispecific molecule 4, where chain fidelity is seen in one direction: the lambda heavy chain with the competing kappa light chain.

Table 11. Mass spectrometry results for multispecific molecule 4.

Fab Pairing	Predicted Mass (Da)	Observed Mass (Da)
Kappa heavy chain/kappa light chain	47634.9	47634.6
Kappa heavy chain/lambda light chain	46880.4	46879.0
Lambda heavy chain/lambda light chain	46779.2	46779.4
Lambda heavy chain/kappa light chain	47481.7	N/A

Example 6

Multispecific molecule 5 comprises an α-CTLA4 arm and an α-CD221 arm. The α-CTLA4 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 168 and a second chain of the amino acid sequence of SEQ ID NO: 106. The α-TRAILR2 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 180 and a second chain of the amino acid sequence of SEQ ID NO: 136. The configuration of multispecific molecule 5 is shown in FIG. 5.

Multispecific molecule 5 was expressed by co-transfecting cells with expression vectors comprising polynucleotide sequences of SEQ ID NO: 78, SEQ ID NO: 15, SEQ ID NO: 88, and SEQ ID NO: 45. Multispecific molecule 5 was purified and a SDS-PAGE gel of the final product is shown in FIG. 14. The mass spectrometry data of the papain cleavage of multispecific molecule 5 is shown in FIG. 33 and summarized in Table 12, where there is one incorrect Fab pairing with the lambda heavy chain paired with the kappa light chain.

Table 12. Mass spectrometry results for multispecific molecule 5.

Fab Pairing	Predicted Mass (Da)	Observed Mass (Da)
Kappa heavy chain/kappa light chain	47634.9	47635.1
Kappa heavy chain/lambda light chain	47652.9	N/A
Lambda heavy chain/lambda light chain	48205.1	48202.3
Lambda heavy chain/kappa light chain	48817.2	48814.3

Example 7

Multispecific molecule 6 comprises an α-PD1 arm and an α-TRAILR2 arm. The α-PD1 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 181 and a second chain of the amino acid sequence of SEQ ID NO: 182. The α-TRAILR2 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 177 and a second chain of the amino acid sequence of SEQ ID NO: 148. The configuration of multispecific molecule 6 is shown in FIG. 5.

Multispecific molecule 6 was expressed by co-transfecting cells with expression vectors comprising polynucleotide sequences of SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 81, and SEQ ID NO: 57. Multispecific molecule 6 was purified and a SDS-PAGE gel of the final product is shown in FIG. 15. The mass spectrometry data of the papain cleavage of multispecific molecule 6 is shown in FIG. 34 and summarized in Table 13, where there is one incorrect Fab pairing with the lambda heavy chain paired with the kappa light chain.

Table 13. Mass spectrometry results for multispecific molecule 6.

Fab Pairing	Predicted Mass (Da)	Observed Mass (Da)
Kappa heavy chain/kappa light chain	46933.9	46934.8
Kappa heavy chain/lambda light chain	46329.6	N/A
Lambda heavy chain/lambda light chain	46779.2	46779.0
Lambda heavy chain/kappa light chain	47400.5	47400.4

Example 8

Multispecific molecule 7 comprises an α-PD1 arm and an α-PDL1 arm. The α-PD1 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 181 and a second chain of the

amino acid sequence of SEQ ID NO: 182. The α-PDL1 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 166 and a second chain of the amino acid sequence of SEQ ID NO: 167. The configuration of multispecific molecule 7 is shown in FIG. 5.

Multispecific molecule 7 was expressed by co-transfecting cells with expression vectors comprising polynucleotide sequences of SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 84, and SEQ ID NO: 85. Multispecific molecule 7 was purified and a SDS-PAGE gel of the final product is shown in FIG. 16. The mass spectrometry data of the papain cleavage of multispecific molecule 7 is shown in FIG. 35 and summarized in Table 14, where there is one incorrect Fab pairing with the lambda heavy chain paired with the kappa light chain.

Table 14. Mass spectrometry results for multispecific molecule 7.

Fab Pairing	Predicted Mass (Da)	Observed Mass (Da)
Kappa heavy chain/kappa light chain	46933.9	46933.0
Kappa heavy chain/lambda light chain	46382.56	N/A
Lambda heavy chain/lambda light chain	46882.7	46883.7
Lambda heavy chain/kappa light chain	47469.0	47467.6

Example 9

Multispecific molecule 8 comprises an α-CTLA4 arm, an α-IL12β arm, and an IL-2 polypeptide. The IL-2 polypeptide is fused to the C-terminus of the lambda light chain of the α-IL12β arm. The α-CTLA4 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 171 and a second chain of the amino acid sequence of SEQ ID NO: 106. The α-IL12β arm, together with the fused IL-2 polypeptide, comprises a first chain of the amino acid sequence of SEQ ID NO: 172 and a second chain of the amino acid sequence of SEQ ID NO: 173. The two heavy chains of multispecific molecule 8 do not comprise the knobs-into-holes mutations. The configuration of multispecific molecule 8 is shown in FIG. 7.

Multispecific molecule 8 was expressed by co-transfecting cells with expression vectors comprising polynucleotide sequences of SEQ ID NO: 73, SEQ ID NO: 15, SEQ ID NO: 74, and SEQ ID NO: 75. Multispecific molecule 8 was purified and a SDS-PAGE gel of the final product is shown in FIG. 17. FIG. 21 shows the size exclusion chromatogram of multispecific molecule 8. A KappaSelect and LambdaFabSelect analysis was performed with multispecific

molecule 8, shown in FIG. 26. Both the KappaSelect and LambdaFabSelect flow-through fractions contained no protein, suggesting good chain fidelity.

Example 10

Multispecific molecule 9 comprises an α-CTLA4 arm, an α-IL12β arm, and an IL-2 polypeptide. The IL-2 polypeptide is fused to the C-terminus of the lambda light chain of the α-IL12β arm. The α-CTLA4 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 168 and a second chain of the amino acid sequence of SEQ ID NO: 106. The α-IL12β arm, together with the fused IL-2 polypeptide, comprises a first chain of the amino acid sequence of SEQ ID NO: 170 and a second chain of the amino acid sequence of SEQ ID NO: 173. Different from multispecific molecule 8, the two heavy chains of multispecific molecule 9 comprise the knobs-into-holes mutations. The configuration of multispecific molecule 9 is shown in FIG. 6.

Multispecific molecule 9 was expressed by co-transfecting cells with expression vectors comprising polynucleotide sequences of SEQ ID NO: 78, SEQ ID NO: 15, SEQ ID NO: 91, and SEQ ID NO: 75. Multispecific molecule 9 was purified and a SDS-PAGE gel of the final product is shown in FIG. 18. FIG. 22 shows the size exclusion chromatogram of multispecific molecule 9. A KappaSelect and LambdaFabSelect analysis was performed with multispecific molecule 9, shown in FIG. 27. Both the KappaSelect and LambdaFabSelect flow-through fractions contained no protein, suggesting good chain fidelity.

Example 11

Multispecific molecule 10 comprises an α-CTLA4 arm, an α-IL12β arm, and two IL-2 polypeptides. The first IL-2 polypeptide is fused to the C-terminus of the lambda light chain of the α-IL12β arm. The second IL-2 polypeptide is fused to the C-terminus of the heavy chain of the α-IL12β arm. The α-CTLA4 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 171 and a second chain of the amino acid sequence of SEQ ID NO: 106. The α-IL12β arm, together with the two fused IL-2 polypeptides, comprises a first chain of the amino acid sequence of SEQ ID NO: 175 and a second chain of the amino acid sequence of SEQ ID NO: 173. The two heavy chains of multispecific molecule 10 do not comprise the knobs-into-holes mutations. The configuration of multispecific molecule 10 is shown in FIG. 9.

Multispecific molecule 10 was expressed by co-transfecting cells with expression vectors comprising polynucleotide sequences of SEQ ID NO: 73, SEQ ID NO: 15, SEQ ID NO: 77, and SEQ ID NO: 75. A KappaSelect and LambdaFabSelect analysis was performed with multispecific molecule 10, shown in FIG. 29. The flow-through from the KappaSelect column contained no protein, while the flow-through from the LambdaFabSelect column had protein primarily composed of the kappa heavy chain (knob) and kappa light chain. This suggests that the expression for the kappa pieces was greater than that of the lambda chains, rather than an issue with chain fidelity.

Example 12

Multispecific molecule 11 comprises an α-CTLA4 arm, an α-IL12β arm, and two IL-2 polypeptides. The first IL-2 polypeptide is fused to the C-terminus of the lambda light chain of the α-IL12β arm. The second IL-2 polypeptide is fused to the C-terminus of the heavy chain of the α-IL12β arm. The α-CTLA4 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 168 and a second chain of the amino acid sequence of SEQ ID NO: 106. The α-IL12β arm, together with the two fused IL-2 polypeptides, comprises a first chain of the amino acid sequence of SEQ ID NO: 174 and a second chain of the amino acid sequence of SEQ ID NO: 173. Different from multispecific molecule 10, the two heavy chains of multispecific molecule 11 comprise the knobs-into-holes mutations. The configuration of multispecific molecule 11 is shown in FIG. 8.

Multispecific molecule 11 was expressed by co-transfecting cells with expression vectors comprising polynucleotide sequences of SEQ ID NO: 78, SEQ ID NO: 15, SEQ ID NO: 76, and SEQ ID NO: 75. A KappaSelect and LambdaFabSelect analysis was performed with multispecific molecule 11, shown in FIG. 28. The flow-through from the KappaSelect column contained no protein, while the flow-through from the LambdaFabSelect column had protein primarily composed of the kappa heavy chain (knob) and kappa light chain. This suggests that the expression for the kappa pieces was greater than that of the lambda chains, rather than an issue with chain fidelity. This agrees with the what was seen with multispecific molecule 10, which is the same molecule except for the absence of the knob-in-hole mutations.

Example 13

Multispecific molecule 12 comprises an α-CTLA4 arm, an α-TRAILR2 arm, a scFv targeting arm, and an IL-2 polypeptide. The IL-2 polypeptide is fused to the C-terminus of the kappa light chain of the α-CTLA4 arm. The scFv is fused to the C-terminus of the heavy chain of the α-CTLA4 arm. The α-CTLA4 arm, together with the fused IL-2 polypeptide and the scFv, comprises a first chain of the amino acid sequence of SEQ ID NO: 169 and a second chain of the amino acid sequence of SEQ ID NO: 176. The α-TRAILR2 arm comprises a first chain of the amino acid sequence of SEQ ID NO: 177 and a second chain of the amino acid sequence of SEQ ID NO: 148. The two heavy chains of multispecific molecule 12 comprise the knobs-into-holes mutations. The configuration of multispecific molecule 12 is shown in FIG. 10.

Multispecific molecule 12 was expressed by co-transfecting cells with expression vectors comprising polynucleotide sequences of SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, and SEQ ID NO: 57. A KappaSelect and LambdaFabSelect analysis was performed with multispecific molecule 12, shown in FIG. 30. The ratios indicate the ratios of DNA used at the time of transfection, varying from 3:1 to 1:3 of kappa to lambda. In all cases, there is protein in the flow-through of both the KappaSelect and LambdaFabSelect columns. The protein in the KappaSelect flow-through is composed of the kappa heavy chain, lambda heavy chain, and lambda light chain. The protein in the LambdaFabSelect flow-through is composed of the kappa heavy and light chains and diminishes as the ratio of the lambda chains increases. These data are in agreement with the data from multispecific molecule 4, which has the same Fab components and only shows the lambda light chain pairing with the kappa heavy chain and not vice versa.

We claim:

1. A multispecific antibody molecule comprising:

i) a first antigen-binding domain that binds to a first antigen, wherein the first antigen-binding domain comprises:

a) a first heavy chain polypeptide (HCP1) comprising: a first heavy chain variable region sequence (HCVRS) sufficient that, when paired with i)b) allows the first antigen-binding domain to bind to the first antigen; and

b) a lambda light chain polypeptide (LLCP) comprising: a lambda light chain variable region sequence (LLCVRS) sufficient that, when paired with i)a) allows the first antigen-binding domain to bind to the first antigen; and

ii) a second antigen-binding domain that binds to a second antigen, wherein the second antigen-binding domain comprises:

a) a second heavy chain polypeptide (HCP2) comprising: a second heavy chain variable region sequence (HCVRS) sufficient that, when paired with ii)b) allows the second antigen-binding domain to bind to the second antigen; and

b) a kappa light chain polypeptide (KLCP) comprising: a kappa light chain variable region sequence (KLCVRS) sufficient that, when paired with ii)a) allows the second antigen-binding domain to bind to the second antigen, wherein:

1) the first HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a first heavy chain germline sequence selected from column 3 of Table 7, column 2 of Table 8b, or column 2 of Table 5b;

2) the LLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a lambda light chain germline sequence selected from column 4 of Table 7, column 3 of Table 8b; or column 3 of Table 5b;

3) the second HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a second heavy chain germline sequence selected from column 3 of Table 6, column 5 of Table 8b, or column 4 of Table 5b; or

4) the KLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a kappa light chain germline sequence selected from column 4 of Table 6, column 6 of Table 8b, or column 5 of Table 5b.

2. The multispecific antibody molecule of claim 1, wherein 1) the first HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a first heavy chain germline sequence selected from column 3 of Table 7, column 2 of Table 8b, or column 2 of Table 5b.

3. The multispecific antibody molecule of claim 2, wherein 2) the LLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a lambda light chain germline sequence selected from column 4 of Table 7, column 3 of Table 8b; or column 3 of Table 5b.

4. The multispecific antibody molecule of claim 2 or 3, wherein 3) the second HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a second heavy chain germline sequence selected from column 3 of Table 6, column 5 of Table 8b, or column 4 of Table 5b.

5. The multispecific antibody molecule of any one of claims 2-4, wherein 4) the KLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a kappa light chain germline sequence selected from column 4 of Table 6, column 6 of Table 8b, or column 5 of Table 5b.

6. The multispecific antibody molecule of any one of claims 2-5, wherein the first heavy chain germline sequence and the lambda light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b.

7. The multispecific antibody molecule of any one of claims 2-6, wherein the first heavy chain germline sequence, the lambda light chain germline sequence, and the kappa light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b.

8. The multispecific antibody molecule of any one of claims 2-7, wherein the second heavy chain germline sequence and the kappa light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b.

9. The multispecific antibody molecule of any one of claims 2-8, wherein the second heavy chain germline sequence, the kappa light chain germline sequence, and the lambda light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b.

10. The multispecific antibody molecule of any one of claims 2-9, wherein at least two (e.g., two, three, or all) of the following: the first heavy chain germline sequence, the lambda light chain germline sequence, the second heavy chain germline sequence, and the kappa light chain germline sequence, are selected from a single row of Table 8b or Table 5b.

11. The multispecific antibody molecule of claim 1, wherein 2) the LLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a lambda light chain germline sequence selected from column 4 of Table 7, column 3 of Table 8b; or column 3 of Table 5b.

12. The multispecific antibody molecule of claim 11, wherein 1) the first HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a first heavy chain germline sequence selected from column 3 of Table 7, column 2 of Table 8b, or column 2 of Table 5b.

13. The multispecific antibody molecule of claim 11 or 12, wherein 3) the second HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a second heavy chain germline sequence selected from column 3 of Table 6, column 5 of Table 8b, or column 4 of Table 5b.

14. The multispecific antibody molecule of any one of claims 11-13, wherein 4) the KLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a kappa light chain germline sequence selected from column 4 of Table 6, column 6 of Table 8b, or column 5 of Table 5b.

15. The multispecific antibody molecule of any one of claims 11-14, wherein the first heavy chain germline sequence and the lambda light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b.

16. The multispecific antibody molecule of any one of claims 11-15, wherein the first heavy chain germline sequence, the lambda light chain germline sequence, and the kappa light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b.

17. The multispecific antibody molecule of any one of claims 11-16, wherein the second heavy chain germline sequence and the kappa light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b.

18. The multispecific antibody molecule of any one of claims 11-17, wherein the second heavy chain germline sequence, the kappa light chain germline sequence, and the lambda light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b.

19. The multispecific antibody molecule of any one of claims 11-18, wherein at least two (e.g., two, three, or all) of the following: the first heavy chain germline sequence, the lambda light chain germline sequence, the second heavy chain germline sequence, and the kappa light chain germline sequence, are selected from a single row of Table 8b or Table 5b.

20. The multispecific antibody molecule of claim 1, wherein 3) the second HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a second heavy chain germline sequence selected from column 3 of Table 6, column 5 of Table 8b, or column 4 of Table 5b.

21. The multispecific antibody molecule of claim 20, wherein 1) the first HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a first heavy chain germline sequence selected from column 3 of Table 7, column 2 of Table 8b, or column 2 of Table 5b.

22. The multispecific antibody molecule of claim 20 or 21, wherein 2) the LLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a lambda light chain germline sequence selected from column 4 of Table 7, column 3 of Table 8b; or column 3 of Table 5b.

23. The multispecific antibody molecule of any one of claims 20-22, wherein 4) the KLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a kappa light chain germline sequence selected from column 4 of Table 6, column 6 of Table 8b, or column 5 of Table 5b.

24. The multispecific antibody molecule of any one of claims 20-23, wherein the first heavy chain germline sequence and the lambda light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b.

25. The multispecific antibody molecule of any one of claims 20-24, wherein the first heavy chain germline sequence, the lambda light chain germline sequence, and the kappa light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b.

26. The multispecific antibody molecule of any one of claims 20-25, wherein the second heavy chain germline sequence and the kappa light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b.

27. The multispecific antibody molecule of any one of claims 20-26, wherein the second heavy chain germline sequence, the kappa light chain germline sequence, and the lambda light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b.

28. The multispecific antibody molecule of any one of claims 20-27, wherein at least two (e.g., two, three, or all) of the following: the first heavy chain germline sequence, the lambda light chain germline sequence, the second heavy chain germline sequence, and the kappa light chain germline sequence, are selected from a single row of Table 8b or Table 5b.

29. The multispecific antibody molecule of claim 1, wherein 4) the KLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a kappa light chain germline sequence selected from column 4 of Table 6, column 6 of Table 8b, or column 5 of Table 5b.

30. The multispecific antibody molecule of claim 29, wherein 1) the first HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a first heavy chain germline sequence selected from column 3 of Table 7, column 2 of Table 8b, or column 2 of Table 5b.

31. The multispecific antibody molecule of claim 29 or 30, wherein 2) the LLCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a lambda light chain germline sequence selected from column 4 of Table 7, column 3 of Table 8b; or column 3 of Table 5b.

32. The multispecific antibody molecule of any one of claims 29-31, wherein 3) the second HCVRS has at least 75, 80, 85, 90, 95, 98, or 100% sequence identity with a second heavy chain germline sequence selected from column 3 of Table 6, column 5 of Table 8b, or column 4 of Table 5b.

33. The multispecific antibody molecule of any one of claims 29-32, wherein the first heavy chain germline sequence and the lambda light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b.

34. The multispecific antibody molecule of any one of claims 29-33, wherein the first heavy chain germline sequence, the lambda light chain germline sequence, and the kappa light chain germline sequence are selected from a single row of Table 7, Table 8b, or Table 5b.

35. The multispecific antibody molecule of any one of claims 29-34, wherein the second heavy chain germline sequence and the kappa light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b.

36. The multispecific antibody molecule of any one of claims 29-35, wherein the second heavy chain germline sequence, the kappa light chain germline sequence, and the lambda light chain germline sequence are selected from a single row of Table 6, Table 8b, or Table 5b.

37. The multispecific antibody molecule of any one of claims 29-36, wherein at least two (e.g., two, three, or all) of the following: the first heavy chain germline sequence, the lambda light chain germline sequence, the second heavy chain germline sequence, and the kappa light chain germline sequence, are selected from a single row of Table 8b or Table 5b.

38. The multispecific antibody molecule of any one of claims 1-37, wherein the first heavy chain germline sequence, the lambda light chain germline sequence, the second heavy chain germline sequence, and the kappa light chain germline sequence are selected from a single row of Table 8b or Table 5b.

39. A multispecific antibody molecule comprising:

i) a first antigen-binding domain that binds to a first antigen, wherein the first antigen-binding domain comprises:

a) a first heavy chain polypeptide (HCP1) comprising: a first heavy chain variable region sequence (HCVRS) sufficient that, when paired with i)b) allows the first antigen-binding domain to bind to the first antigen; and

b) a lambda light chain polypeptide (LLCP) comprising: a lambda light chain variable region sequence (LLCVRS) sufficient that, when paired with i)a) allows the first antigen-binding domain to bind to the first antigen; and

ii) a second antigen-binding domain that binds to a second antigen, wherein the second antigen-binding domain comprises:

a) a second heavy chain polypeptide (HCP2) comprising: a second heavy chain variable region sequence (HCVRS) sufficient that, when paired with ii)b) allows the second antigen-binding domain to bind to the second antigen; and

b) a kappa light chain polypeptide (KLCP) comprising: a kappa light chain variable region sequence (KLCVRS) sufficient that, when paired with ii)a) allows the second antigen-binding domain to bind to the second antigen, wherein:

the multispecific antibody molecule further comprises an accessory moiety, wherein the accessory moiety has a property chosen from:

1) the accessory moiety has a molecular weight of at least 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 kDa;

2) the accessory moiety comprises a polypeptide having at least 30, 40, 50, 60, 70, 80, 90, or 100 amino acid residues;

3) the accessory moiety comprises a polypeptide having the ability to modulate the activity of an immune cell, e.g., a T cell, a B cell, an antigen presenting cell (APC), or an NK cell; or

4) the accessory moiety is chosen from one or more of an immune cell engager (e.g., a CD40 agonist, e.g., a CD40L polypeptide or an agonistic anti-CD40 antibody molecule, or a PD-1 binding moiety, e.g., a PD-1 binding sequence of PDL-1 or an anti-PD-1 antibody molecule), a cytokine molecule (e.g. an IL-2 molecule), a cytokine antagonist (e.g., a TGF-β antagonist), an enzyme, a toxin, or a labeling agent.

40. The multispecific antibody molecule of any one of claims 1-38, wherein the multispecific antibody molecule further comprises an accessory moiety, wherein the accessory moiety has a property chosen from:

1) the accessory moiety has a molecular weight of at least 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 kDa;

2) the accessory moiety comprises a polypeptide having at least 30, 40, 50, 60, 70, 80, 90, or 100 amino acid residues;

3) the accessory moiety comprises a polypeptide having the ability to modulate the active of an immune cell, e.g., a T cell, a B cell, an antigen presenting cell (APC), or an NK cell; or

4) the accessory moiety is chosen from one or more of an immune cell engager (e.g., a CD40 agonist, e.g., a CD40L polypeptide or an agonistic anti-CD40 antibody molecule, or a PD-1 binding moiety, e.g., a PD-1 binding sequence of PDL-1 or an anti-PD-1 antibody molecule), a cytokine molecule (e.g. an IL-2 molecule), a cytokine antagonist (e.g., a TGF-β antagonist), an enzyme, a toxin, or a labeling agent.

41. The multispecific antibody molecule of claim 39 or 40, wherein the accessory moiety is fused to the polypeptide of a , b, c, or d of the multispecific antibody molecule.

42. The multispecific antibody molecule of any one of claims 39-41, wherein the accessory moiety is fused to any of the following: the HCP1, first HCVRS, LLCP, LLCVRS, HCP2, second HCVRS, KLCP, or KLCVRS of the multispecific antibody molecule, e.g., the C-terminus or N-terminus of HCP1, first HCVRS, LLCP, LLCVRS, HCP2, second HCVRS, KLCP, or KLCVRS of the multispecific antibody molecule.

43. The multispecific antibody molecule of any one of claims 39-41, wherein the HCP1 comprises a first heavy chain constant region sequence (HCCRS) (e.g., CH1, CH2, and CH3 sequences), wherein the accessory moiety is fused to the first HCCRS, e.g., the C-terminus of the first HCCRS.

44. The multispecific antibody molecule of any one of claims 39-41, wherein the HCP2 comprises a second heavy chain constant region sequence (HCCRS) (e.g., CH1, CH2, and CH3 sequences), wherein the accessory moiety is fused to the second HCCRS, e.g., the C-terminus of the second HCCRS.

45. The multispecific antibody molecule of any one of claims 39-41, wherein the LLCP comprises a lambda light chain constant region sequence (LLCCRS), wherein the accessory moiety is fused to the LLCCRS, e.g., the C-terminus of the LLCCRS.

46. The multispecific antibody molecule of any one of claims 39-41, wherein the KLCP comprises a kappa light chain constant region sequence (KLCCRS), wherein the accessory moiety is fused to the KLCCRS, e.g., the C-terminus of the KLCCRS.

47. The multispecific antibody molecule of any one of claims 39-46, comprising a first accessory moiety and a second accessory moiety, wherein the first or second accessory moiety has a property chosen from:

1) the first or second accessory moiety has a molecular weight of at least 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 kDa;

2) the first or second accessory moiety comprises a polypeptide having at least 30, 40, 50, 60, 70, 80, 90, or 100 amino acid residues;

3) the first or second accessory moiety comprises a polypeptide having the ability to modulate the active of an immune cell, e.g., a T cell, a B cell, an antigen presenting cell (APC), or an NK cell; or

4) the first or second accessory moiety is chosen from one or more of an immune cell engager (e.g., a CD40 agonist, e.g., a CD40L polypeptide or an agonistic anti-CD40 antibody molecule, or a PD-1 binding moiety, e.g., a PD-1 binding sequence of PDL-1 or an anti-PD-1

antibody molecule), a cytokine molecule (e.g. an IL-2 molecule), a cytokine antagonist (e.g., a TGF-β antagonist), an enzyme, a toxin, or a labeling agent.

48. The multispecific antibody molecule of claim 47, wherein the first and second accessory moieties are the same.

49. The multispecific antibody molecule of claim 47, wherein the first and second accessory moieties are different.

50. The multispecific antibody molecule of any one of claims 47-49, wherein:

i) the first accessory moiety is fused to the HCP1 or HCP2, e.g., the C-terminus of the HCP1 or HCP2; and

ii) the second accessory moiety is fused to the LLCP or KLCP, e.g., the C-terminus of the LLCP or KLCP.

51. The multispecific antibody molecule of any one of claims 47-50, wherein:

i) the HCP1 comprises a first heavy chain constant region sequence (HCCRS) (e.g., CH1, CH2, and CH3 sequences), wherein the first accessory moiety is fused to the first HCCRS, e.g., the C-terminus of the first HCCRS; and

ii) the LLCP comprises a lambda light chain constant region sequence (LLCCRS), wherein the second accessory moiety is fused to the LLCCRS, e.g., the C-terminus of the LLCCRS.

52. The multispecific antibody molecule of any one of claims 47-50, wherein:

i) the HCP2 comprises a second heavy chain constant region sequence (HCCRS) (e.g., CH1, CH2, and CH3 sequences), wherein the accessory moiety is fused to the second HCCRS, e.g., the C-terminus of the second HCCRS; and

ii) the KLCP comprises a kappa light chain constant region sequence (KLCCRS), wherein the accessory moiety is fused to the KLCCRS, e.g., the C-terminus of the KLCCRS.

53. A multispecific antibody molecule comprising:

i) a first antigen-binding domain that binds to a first antigen, wherein the first antigen-binding domain comprises:

a) a first heavy chain polypeptide (HCP1) comprising: a first heavy chain variable region sequence (HCVRS) sufficient that, when paired with i)b) allows the first antigen-binding domain to bind to the first antigen; and a first heavy chain constant region sequence (HCCRS) (e.g., a first CH1 sequence), and

b) a lambda light chain polypeptide (LLCP) comprising: a lambda light chain variable region sequence (LLCVRS) sufficient that, when paired with i)a) allows the first antigen-binding domain to bind to the first antigen; and a lambda light chain constant region sequence (LLCCRS), and

ii) a second antigen-binding domain that binds to a second antigen, wherein the second antigen-binding domain comprises:

a) a second heavy chain polypeptide (HCP2) comprising: a second heavy chain variable region sequence (HCVRS) sufficient that, when paired with ii)b) allows the second antigen-binding domain to bind to the second antigen; and a second heavy chain constant region sequence (HCCRS) (e.g., a second CH1 sequence) and

b) a kappa light chain polypeptide (KLCP) comprising: a kappa light chain variable region sequence (KLCVRS) sufficient that, when paired with ii)a) allows the second antigen-binding domain to bind to the second antigen; and a kappa light chain constant region sequence (KLCCRS), wherein:

1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation, or the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation; and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation, or the multispecific antibody molecule does not

comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation.

54. The multispecific antibody molecule of any one of claims 1-52, wherein

i)a) the HCP1 comprises a first heavy chain constant region sequence (HCCRS) (e.g., a first CH1 sequence),

i)b) the LLCP comprises a lambda light chain constant region sequence (LLCCRS),

ii)a) the HCP2 comprises a second heavy chain constant region sequence (HCCRS) (e.g., a second CH1 sequence), and

ii)b) the KLCP comprises a kappa light chain constant region sequence (KLCCRS), wherein:

1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation, or the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence) that promotes the preferential pairing of the HCP1 and the LLCP, compared with pairing of the HCP1 and the LLCP without the mutation; and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation, or the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence) that promotes the preferential pairing of the HCP2 and the KLCP, compared with pairing of the HCP2 and the KLCP without the mutation.

55. The multispecific antibody molecule of claim 53 or 54, wherein the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that increases the preferential pairing of the HCP1 and the LLCP by at least 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or 50 folds, compared

with pairing of the HCP1 and the LLCP without the mutation, or the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence) that increases the preferential pairing of the HCP1 and the LLCP by at least 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or 50 folds, compared with pairing of the HCP1 and the LLCP without the mutation.

56. The multispecific antibody molecule of any one of claims 53-55, wherein the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence) that increases the preferential pairing of the HCP2 and the KLCP by at least 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or 50 folds, compared with pairing of the HCP2 and the KLCP without the mutation, or the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence) that increases the preferential pairing of the HCP2 and the KLCP by at least 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or 50 folds, compared with pairing of the HCP2 and the KLCP without the mutation.

57. A multispecific antibody molecule comprising:

i) a first antigen-binding domain that binds to a first antigen, wherein the first antigen-binding domain comprises:

a) a first heavy chain polypeptide (HCP1) comprising: a first heavy chain variable region sequence (HCVRS) sufficient that, when paired with i)b) allows the first antigen-binding domain to bind to the first antigen; and a first heavy chain constant region sequence (HCCRS) (e.g., a first CH1 sequence), and

b) a lambda light chain polypeptide (LLCP) comprising: a lambda light chain variable region sequence (LLCVRS) sufficient that, when paired with i)a) allows the first antigen-binding domain to bind to the first antigen; and a lambda light chain constant region sequence (LLCCRS), and

ii) a second antigen-binding domain that binds to a second antigen, wherein the second antigen-binding domain comprises:

a) a second heavy chain polypeptide (HCP2) comprising: a second heavy chain variable region sequence (HCVRS) sufficient that, when paired with ii)b) allows the

second antigen-binding domain to bind to the second antigen; and a second heavy chain constant region sequence (HCCRS) (e.g., a second CH1 sequence) and

b) a kappa light chain polypeptide (KLCP) comprising: a kappa light chain variable region sequence (KLCVRS) sufficient that, when paired with ii)a) allows the second antigen-binding domain to bind to the second antigen; and a kappa light chain constant region sequence (KLCCRS), wherein:

1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence), or the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence); and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence), or the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence).

58. The multispecific antibody molecule of any one of claims 1-56, comprising:

i)a) the HCP1 comprises a first heavy chain constant region sequence (HCCRS) (e.g., a first CH1 sequence),

i)b) the LLCP comprises a lambda light chain constant region sequence (LLCCRS),

ii)a) the HCP2 comprises a second heavy chain constant region sequence (HCCRS) (e.g., a second CH1 sequence), and

ii)b) the KLCP comprises a kappa light chain constant region sequence (KLCCRS), wherein:

1) the multispecific antibody molecule does not comprise a mutation in the first HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence), or the multispecific antibody molecule does not comprise a mutation in the LLCCRS (e.g., a mutation relative to a naturally existing lambda light chain constant region sequence); and

2) the multispecific antibody molecule does not comprise a mutation in the second HCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence), or the multispecific antibody molecule does not comprise a mutation in the KLCCRS (e.g., a mutation relative to a naturally existing kappa light chain constant region sequence).

59. The multispecific antibody molecule of claim 57 or 58, wherein the multispecific antibody molecule does not comprise a mutation in any of the following: the first HCCRS, the LLCCRS, the second HCCRS, and the KLCCRS (e.g., a mutation relative to a naturally existing heavy chain constant region sequence, a naturally existing lambda light chain constant region sequence, or a naturally existing kappa light chain constant region sequence).

60. A multispecific antibody molecule comprising:

i) a first antigen-binding domain that binds to a first antigen, wherein the first antigen-binding domain comprises:

a) a first heavy chain polypeptide (HCP1) comprising: a first heavy chain variable region sequence (HCVRS) sufficient that, when paired with i)b) allows the first antigen-binding domain to bind to the first antigen; and a first heavy chain constant region sequence (HCCRS) (e.g., a first CH1 sequence), and

b) a lambda light chain polypeptide (LLCP) comprising: a lambda light chain variable region sequence (LLCVRS) sufficient that, when paired with i)a) allows the first antigen-binding domain to bind to the first antigen; and a lambda light chain constant region sequence (LLCCRS), and

ii) a second antigen-binding domain that binds to a second antigen, wherein the second antigen-binding domain comprises:

a) a second heavy chain polypeptide (HCP2) comprising: a second heavy chain variable region sequence (HCVRS) sufficient that, when paired with ii)b) allows the second antigen-binding domain to bind to the second antigen; and a second heavy chain constant region sequence (HCCRS) (e.g., a second CH1 sequence) and

b) a kappa light chain polypeptide (KLCP) comprising: a kappa light chain variable region sequence (KLCVRS) sufficient that, when paired with ii)a) allows the second antigen-binding domain to bind to the second antigen; and a kappa light chain constant region sequence (KLCCRS), wherein:

1) the first HCCRS comprises a naturally existing heavy chain constant region sequence, or the LLCCRS comprises a naturally existing lambda light chain constant region sequence; and

2) the second HCCRS comprises a naturally existing heavy chain constant region sequence, or the KLCCRS comprises a naturally existing kappa light chain constant region sequence.

61. The multispecific antibody molecule of any one of claims 1-59, wherein:

i)a) the HCP1 comprises a first heavy chain constant region sequence (HCCRS) (e.g., a first CH1 sequence),

i)b) the LLCP comprises a lambda light chain constant region sequence (LLCCRS),

ii)a) the HCP2 comprises a second heavy chain constant region sequence (HCCRS) (e.g., a second CH1 sequence), and

ii)b) the KLCP comprises a kappa light chain constant region sequence (KLCCRS), wherein:

1) the first HCCRS comprises a naturally existing heavy chain constant region sequence, or the LLCCRS comprises a naturally existing lambda light chain constant region sequence; and

2) the second HCCRS comprises a naturally existing heavy chain constant region sequence, or the KLCCRS comprises a naturally existing kappa light chain constant region sequence.

62. The multispecific antibody molecule of claim 60 or 61, wherein:

i) the first HCCRS comprises a naturally existing heavy chain constant region sequence,

ii) the LLCCRS comprises a naturally existing lambda light chain constant region sequence,

iii) the second HCCRS comprises a naturally existing heavy chain constant region sequence, and

iv) the KLCCRS comprises a naturally existing kappa light chain constant region sequence.

63. The multispecific antibody molecule of any one of claims 1-62, wherein the HCP1 preferentially binds to the LLCP over the KLCP.

64. The multispecific antibody molecule of any one of claims 1-63, wherein the LLCP preferentially binds to the HCP1 over the HCP2.

65. The multispecific antibody molecule of any one of claims 1-64, wherein the HCP2 preferentially binds to the KLCP over the LLCP.

66. The multispecific antibody molecule of any one of claims 1-65, wherein the KLCP preferentially binds to the HCP2 over the HCP1.

67. The multispecific antibody molecule of any one of claims 1-66, wherein the HCP1 has a higher affinity, e.g., a substantially higher affinity, for the LLCP than for the KLCP (e.g., the K_D for the binding between the HCP1 and the LLCP is no more than 50%, 40%, 30%, 20%, 10%, 1%, 0.1%, or 0.01% of the K_D for the binding between the HCP1 and the KLCP).

68. The multispecific antibody molecule of any one of claims 1-67, wherein the LLCP has a higher affinity, e.g., a substantially higher affinity, for the HCP1 than for the HCP2 (e.g., the K_D for the binding between the LLCP and the HCP1 is no more than 50%, 40%, 30%, 20%, 10%, 1%, 0.1%, or 0.01% of the K_D for the binding between the LLCP and the first HCP2).

69. The multispecific antibody molecule of any one of claims 1-68, wherein the HCP2 has a higher affinity, e.g., a substantially higher affinity, for the KLCP than for the LLCP (e.g., the K_D for the binding between the HCP2 and the KLCP is no more than 50%, 40%, 30%, 20%, 10%, 1%, 0.1%, or 0.01% of the K_D for the binding between the HCP2 and the LLCP).

70. The multispecific antibody molecule of any one of claims 1-69, wherein the KLCP has a higher affinity, e.g., a substantially higher affinity, for the HCP2 than for the HCP1 (e.g., the K_D for the binding between the KLCP and the HCP2 is no more than 50%, 40%, 30%, 20%, 10%, 1%, 0.1%, or 0.01% of the K_D for the binding between the KLCP and the HCP1).

71. The multispecific antibody molecule of any one of claims 1-70, wherein the percent binding between the HCP1 and the LLCP in the presence of the KLCP is at least 75, 80, 90, 95, 98, 99, or 99.5%.

72. The multispecific antibody molecule of any one of claims 1-71, wherein the percent binding between the HCP1 and the LLCP in the presence of the HCP2 is at least 75, 80, 90, 95, 98, 99, or 99.5%.

73. The multispecific antibody molecule of any one of claims 1-72, wherein the percent binding between the HCP2 and the KLCP in the presence of the LLCP is at least 75, 80, 90, 95, 98, 99, or 99.5%.

74. The multispecific antibody molecule of any one of claims 1-73, wherein the percent binding between the HCP2 and the KLCP in the presence of the HCP1 is at least 75, 80, 90, 95, 98, 99, or 99.5%.

75. The multispecific antibody molecule of any one of claims 1-74, wherein when the HCP1, LLCP, HCP2, and KLCP are present under preselected conditions, e.g., in aqueous buffer, e.g., at pH 7, in saline, e.g., at pH 7, or under physiological conditions:

i) at least 70, 75, 80, 90, 95, 98, 99, 99.5, or 99.9 % of the HCP1 is complexed, or interfaced with, the LLCP;

ii) at least 70, 75, 80, 90, 95, 98, 99, 99.5, or 99.9 % of the LLCP is complexed, or interfaced with, the HCP1;

iii) at least 70, 75, 80, 90, 95, 98, 99, 99.5, or 99.9 % of the HCP2 is complexed, or interfaced with, the KLCP; or

iv) at least 70, 75, 80, 90, 95, 98, 99, 99.5, or 99.9 % of the KLCP is complexed, or interfaced with, the HCP2.

76. The multispecific antibody molecule of any one of claims 1-75, wherein the HCP1 is complexed, or interfaced with, the HCP2.

77. The multispecific antibody molecule of any one of claims 1-76, wherein the HCP1 has a greater affinity, e.g., a substantially greater affinity, for HCP2, than for a second molecule of HCP1.

78. The multispecific antibody molecule of any one of claims 1-77, wherein the HCP2 has a greater affinity, e.g., a substantially greater affinity, for HCP1, than for a second molecule of HCP2.

79. The multispecific antibody molecule of any one of claims 1-78, wherein the HCP1 comprises a sequence element that increases the ratio of HCP1-HCP2: HCP1-HCP1 pairings, compared to the ratio that would be seen in the absence of the sequence element, e.g., where a naturally occurring sequence replaces the sequence element.

80. The multispecific antibody molecule of any one of claims 1-79, wherein the HCP2 comprises a sequence element that increases the ratio of HCP1-HCP2: HCP2-HCP2 pairings, compared to the ratio that would be seen in the absence of the sequence element, e.g., where a naturally occurring sequence replaces the sequence element.

81. The multispecific antibody of claims 79 or 80, wherein the sequence element is not a naturally occurring constant region sequence.

82. The multispecific antibody of claims 79 or 80, wherein the sequence element is disposed in CH3.

83. The multispecific antibody of any one of claims 1-82, wherein one or both of HCP1 and HCP2 were selected to minimize self-dimerization (e.g., HCP1-HCP1) as opposed to heterodimerization (e.g., HCP2-HCP2).

84. The multispecific antibody molecule of any one of claims 1-83, wherein HCP1 and HCP2 are members of a paired protuberance/cavity, e.g., knob and hole pair.

85. The multispecific antibody molecule of any one of claims 1-83, wherein HCP1-HCP2 paring is promoted by an electrostatic interaction.

86. The multispecific antibody molecule of any one of claims 1-83, wherein HCP1-HCP2 paring is promoted by strand exchange.

87. The multispecific antibody molecule of any one of claims 1-83, wherein HCP1 and HCP2 are not members of a paired protuberance/cavity, e.g., knob and hole pair.

88. The multispecific antibody molecule of any one of claims 1-76, wherein the HCP1 comprises a first heavy chain constant region sequence (HCCRS), wherein the first HCCRS does not comprise a mutation (e.g., a mutation relative to a naturally existing heavy chain constant region sequence).

89. The multispecific antibody molecule of any one of claims 1-76, wherein the HCP2 comprises a second heavy chain constant region sequence (HCCRS), wherein the second HCCRS does not comprise a mutation (e.g., a mutation relative to a naturally existing heavy chain constant region sequence).

90. The multispecific antibody molecule of any one of claims 1-76, wherein:

i) the HCP1 comprises a first heavy chain constant region sequence (HCCRS), wherein the first HCCRS does not comprise a mutation (e.g., a mutation relative to a naturally existing heavy chain constant region sequence); and

ii) the HCP2 comprises a second heavy chain constant region sequence (HCCRS), wherein the second HCCRS does not comprise a mutation (e.g., a mutation relative to a naturally existing heavy chain constant region sequence).

91. The multispecific antibody molecule of any one of claims 1-76, wherein the HCP1 comprises a first CH2 domain sequence and a first CH3 domain sequence, wherein the first CH2 domain sequence and the first CH3 domain sequence do not comprise a mutation (e.g., a mutation

relative to a naturally existing CH2 domain sequence or a naturally existing CH3 domain sequence).

92. The multispecific antibody molecule of any one of claims 1-76, wherein the HCP2 comprises a second CH2 domain sequence and a second CH3 domain sequence, wherein the second CH2 domain sequence and the second CH3 domain sequence do not comprise a mutation (e.g., a mutation relative to a naturally existing CH2 domain sequence or a naturally existing CH3 domain sequence).

93. The multispecific antibody molecule of any one of claims 1-76, wherein:

i) the HCP1 comprises a first CH2 domain sequence and a first CH3 domain sequence, wherein the first CH2 domain sequence and the first CH3 domain sequence do not comprise a mutation (e.g., a mutation relative to a naturally existing CH2 domain sequence or a naturally existing CH3 domain sequence); and

ii) the HCP2 comprises a second CH2 domain sequence and a second CH3 domain sequence, wherein the second CH2 domain sequence and the second CH3 domain sequence do not comprise a mutation (e.g., a mutation relative to a naturally existing CH2 domain sequence or a naturally existing CH3 domain sequence).

94. The multispecific antibody molecule of any one of claims 1-93, wherein the HCP1 is derived from an antibody arising, either in vivo or in vitro, as a lambda antibody.

95. The multispecific antibody molecule of any one of claims 1-94, wherein the HCP2 is derived from an antibody arising, either in vivo or in vitro, as a kappa antibody.

96. The multispecific antibody molecule of any one of claims 1-95, wherein the HCP1 and LLCP comprise amino acid sequences selected from Table 18 (e.g., as paired in Table 18) or Table 5a (e.g., as paired in Table 5a), or functional variant or fragment thereof.

97. The multispecific antibody molecule of any one of claims 1-96, wherein the HCP2 and KLCP comprise amino acid sequences selected from Table 18 (e.g., as paired in Table 18) or Table 5a (e.g., as paired in Table 5a), or functional variant or fragment thereof.

98. The multispecific antibody molecule of any one of claims 1-97, wherein the HCP1, LLCP, HCP2, and KLCP comprise amino acid sequences selected from Table 18 (e.g., a single cell of Table 18) or Table 5a (e.g., a single row of Table 5a), or functional variant or fragment thereof.

99. The multispecific antibody molecule of any one of claims 1-98, wherein the first or second antigen is a tumor antigen, e.g., a pancreatic, lung, or colorectal tumor antigen.

100. The multispecific antibody molecule of any one of claims 1-99, wherein the first or second antigen is chosen from: PD-L1, HER3, TROP2, mesothelin, IGF-1R, or CA19-9.

101. The multispecific antibody molecule of any one of claims 1-100, wherein the first or second antigen is chosen from: PD-L1, HER3, TROP2, VEGF-A, EGFR, MUC1, DLL4, or HGF.

102. The multispecific antibody molecule of any one of claims 1-101, wherein the first or second antigen is chosen from: PD-L1, HER3, TROP2, VEGF-A, EGFR, MUC1, MAGE-A3, gpA33, NY-ESO-1, ANG2, RSPO3, HER2, CEACAM5, or CEA.

103. The multispecific antibody molecule of any one of claims 1-102, wherein the first or second antigen is an antigen of an immune effector cell, e.g., a T cell, an NK cell, or a myeloid cell.

104. The multispecific antibody molecule of any one of claims 1-103, wherein the first or second antigen is chosen from: CD3, PD-1, LAG-3, TIM-3, CTLA-4, VISTA, TIGIT, PD-L1, B7-H3, 4-1BB, or ICOS.

105. The multispecific antibody molecule of any one of claims 1-104, wherein the first antigen is a tumor antigen, e.g., mesothelin, and the second antigen is an antigen chosen from NKP30, PD-L1, CD3, NKG2D, CD47, 4-1BB, or NKP46; or the second antigen is a tumor antigen, e.g., mesothelin, and the first antigen is an antigen chosen from NKP30, PD-L1, CD3, NKG2D, CD47, 4-1BB, or NKP46.

106. The multispecific antibody molecule of any one of claims 1-105, wherein the first antigen is IGF1R and the second antigen is HER3, or the second antigen is IGF1R and the first antigen is HER3.

107. The multispecific antibody molecule of any one of claims 1-105, wherein the first antigen is mesothelin and the second antigen is PD-L1, or the second antigen is mesothelin and the first antigen is PD-L1.

108. The multispecific antibody molecule of any one of claims 1-105, wherein the first antigen is CTLA4 and the second antigen is IL12β, or the second antigen is CTLA4 and the first antigen is IL12β.

109. The multispecific antibody molecule of any one of claims 1-105, wherein the first antigen is CTLA4 and the second antigen is TRAILR2, or the second antigen is CTLA4 and the first antigen is TRAILR2.

110. The multispecific antibody molecule of any one of claims 1-105, wherein the first antigen is CTLA4 and the second antigen is CD221, or the second antigen is CTLA4 and the first antigen is CD221.

111. The multispecific antibody molecule of any one of claims 1-105, wherein the first antigen is PD1 and the second antigen is TRAILR2, or the second antigen is PD1 and the first antigen is TRAILR2.

112. The multispecific antibody molecule of any one of claims 1-105, wherein the first antigen is PD1 and the second antigen is PDL1, or the second antigen is PD1 and the first antigen is PDL1.

113. The multispecific antibody molecule of any one of claims 1-105, wherein the first antigen is PD1 and the second antigen is PDL1, or the second antigen is PD1 and the first antigen is PDL1.

114. The multispecific antibody molecule of any one of claims 1-113, further comprising an IL-2 molecule or a CD40 agonist, e.g., a CD40L polypeptide or an agonistic anti-CD40 antibody molecule.

115. A nucleic acid which encodes one, two, three, or all of HCP1, LLCP, HCP2, or KLCP of any one of claims 1-114.

116. A vector comprising the nucleic acid of claim 115.

117. A host cell comprising the nucleic acid of claim 114 or the vector of claim 116.

118. A method of making one, two, three or all of HCP1, LLCP, HCP2, or KLCP, comprising culturing the cell of claim 117, to thereby produce one, two, three or all of HCP1, LLCP, HCP2, or KLCP.

119. A method of making a multispecific antibody molecule comprising HCP1, LLCP, HCP2, and KLCP, e.g., a multispecific antibody molecule of any one of claims 1-114, comprising:

combining HCP1, LLCP, HCP2, and KLCP under conditions suitable for association of HCP1, LLCP, HCP2, and KLCP;

thereby making a multispecific antibody molecule comprising HCP1, LLCP, HCP2, and KLCP.

120. The method of claim 118 or 119, wherein the method produces correctly paired kappa/lambda multispecific antibody molecules in high yield.

121. A preparation comprising the multispecific antibody molecule of any one of claims 1-88.

122. A preparation of multispecific antibody molecules, where at least 50, 60, 70, 80, 90, 95, 98, 99, or 99.9% of the multispecific antibody molecules comprise:

a lambda light chain polypeptide (LLCP) complexed with, or interfaced with, a first heavy chain polypeptide (HCP1); and

a kappa light chain polypeptide (KLCP) complexed with, or interfaced with, a second heavy chain polypeptide (HCP2), wherein:

the HCP1 is complexed with, or interfaced with the HCP2.

123. The preparation of claim 122, wherein the multispecific antibody molecule comprises the multispecific antibody molecule of any one of claims 1-114.

124. The preparation of any one of claims 121-123, wherein the preparation is a pharmaceutically accepted preparation, and, e.g., comprises a pharmaceutically acceptable diluent or excipient.

125. A pharmaceutical composition comprising the multispecific antibody molecule of any one of claims 1-114 and a pharmaceutically acceptable diluent or excipient.

126. A method of providing a subject with a multispecific antibody molecule, comprising:

providing the subject with a pharmaceutical preparation comprising the multispecific antibody molecule of any one of claims 1-114.

127. A method of treating a subject in need thereof, the method comprising: administering to the subject an effective amount of the multispecific antibody molecule of any one of claims 1-114 or the pharmaceutical composition of claim 125.

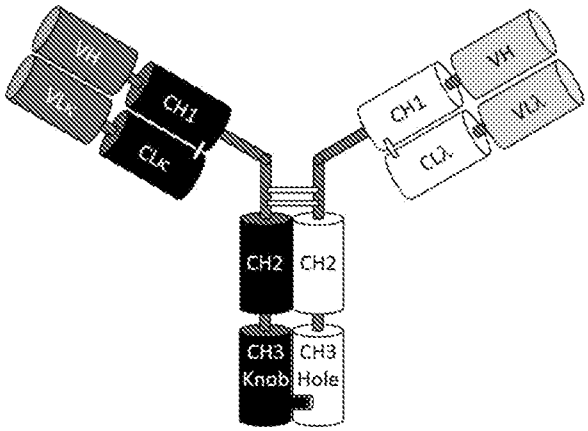


FIG. 1A

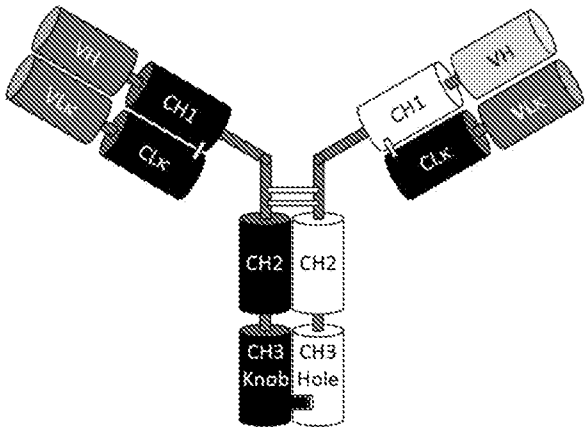


FIG. 1B

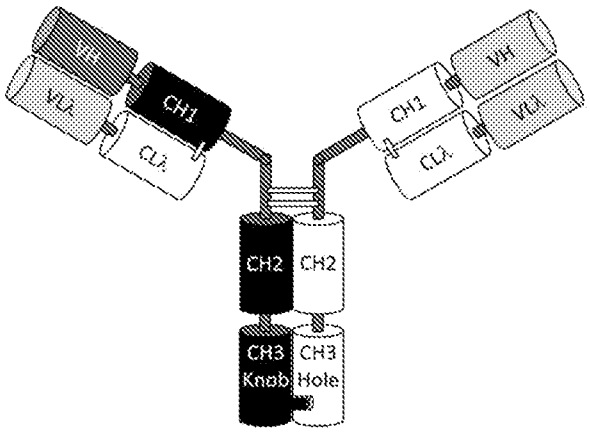


FIG. 1C

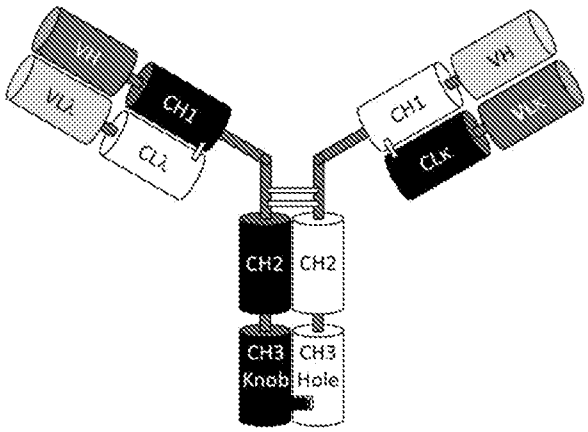
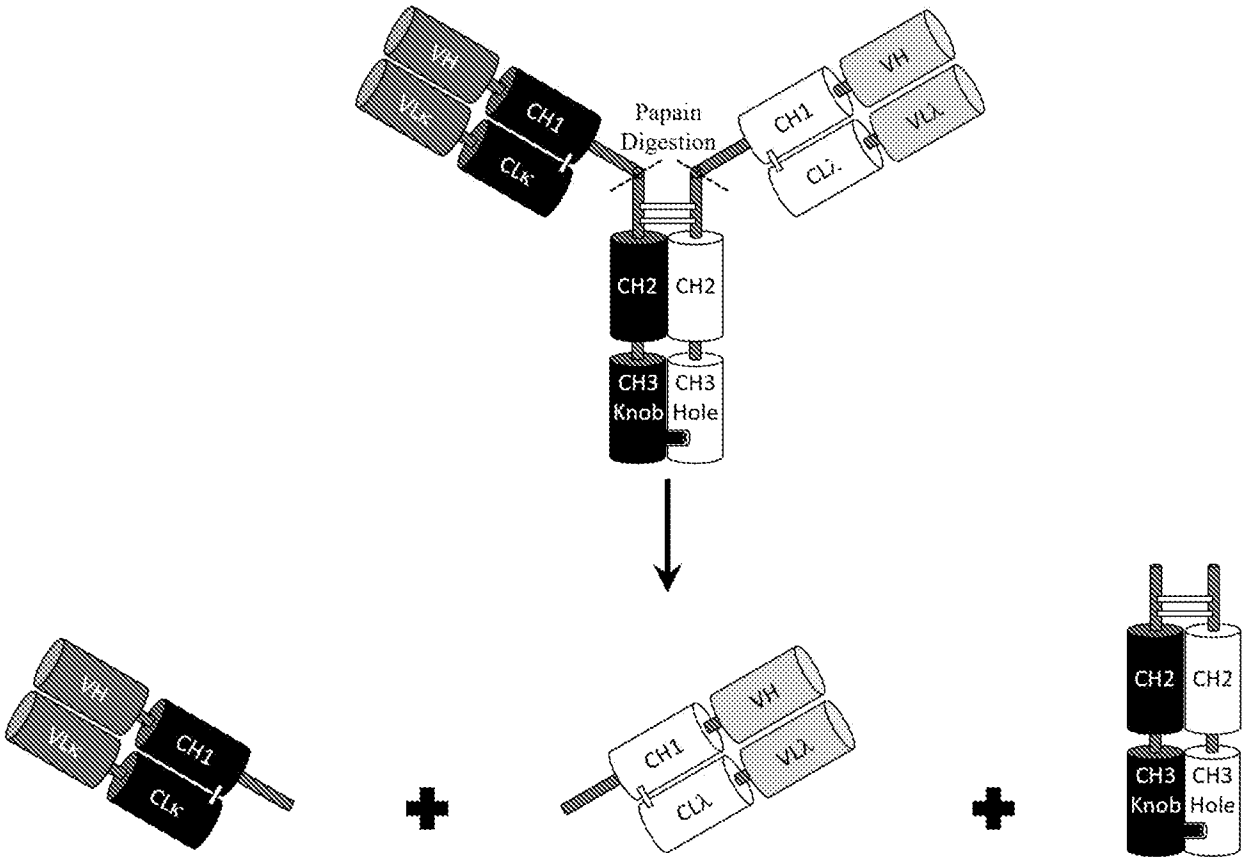


FIG. 1D


VH
VL
CH1
CLκ
Papain
Digestion
CH1
VH
VLλ
CLλ
CH2
CH2
CH3
Knob
CH3
Hole
VH
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CH2
CH2
CH3
Knob
CH3
Hole

FIG. 2

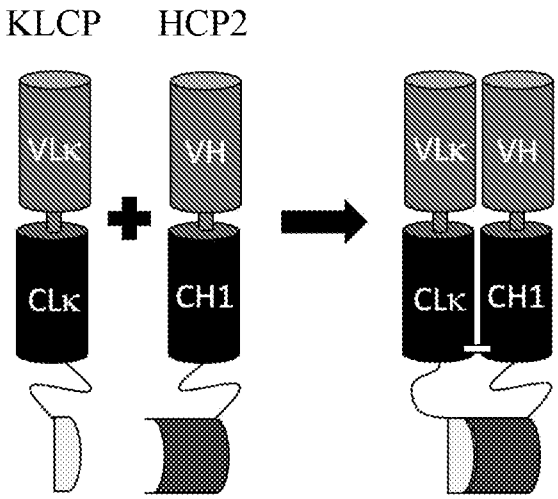


FIG. 3A

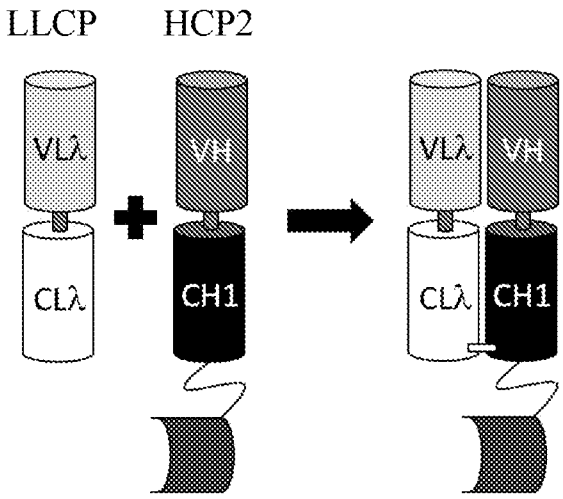


FIG. 3B

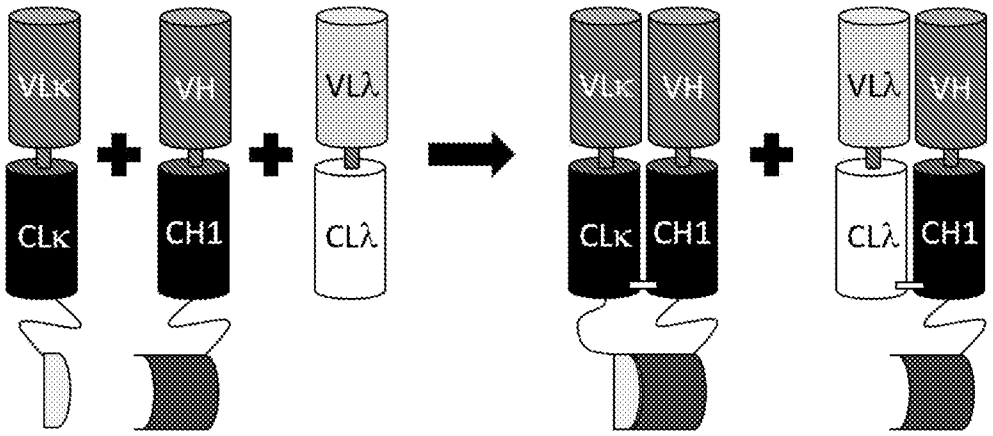


FIG. 3C

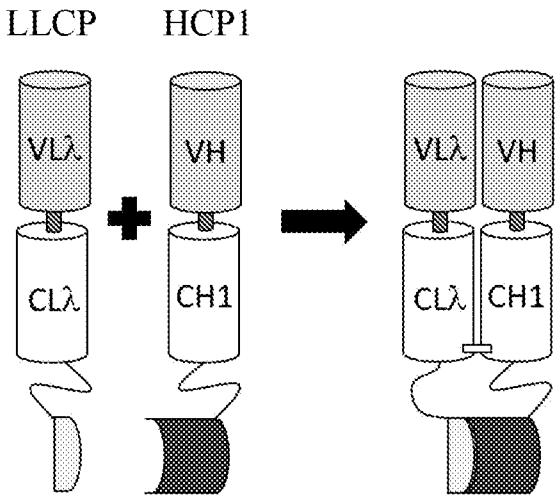


FIG. 4A

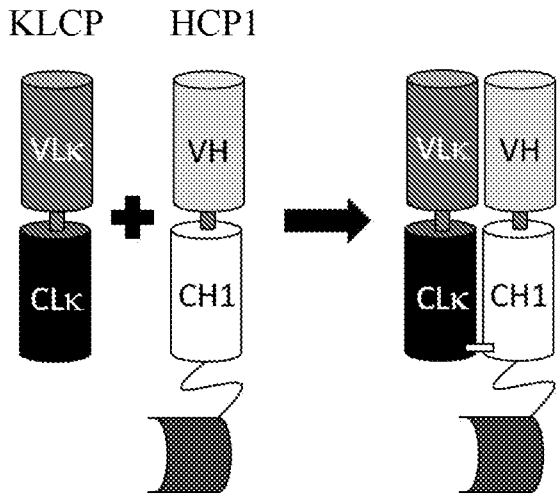


FIG. 4B

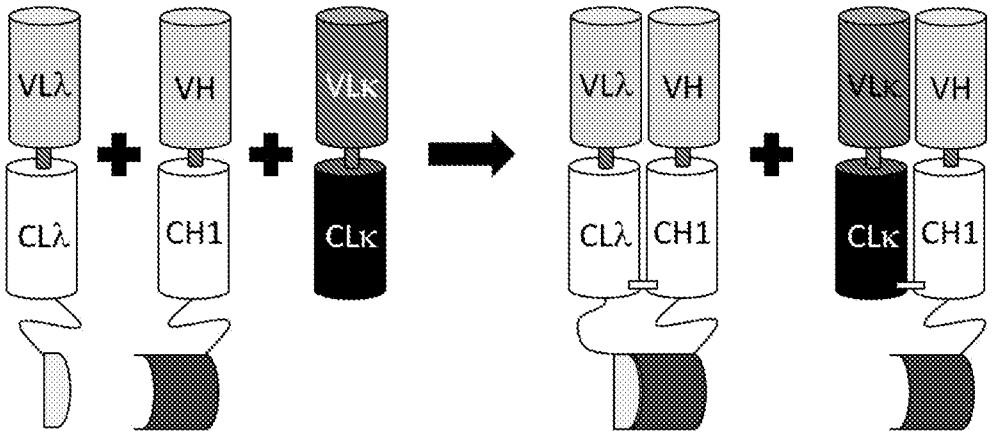


FIG. 4C

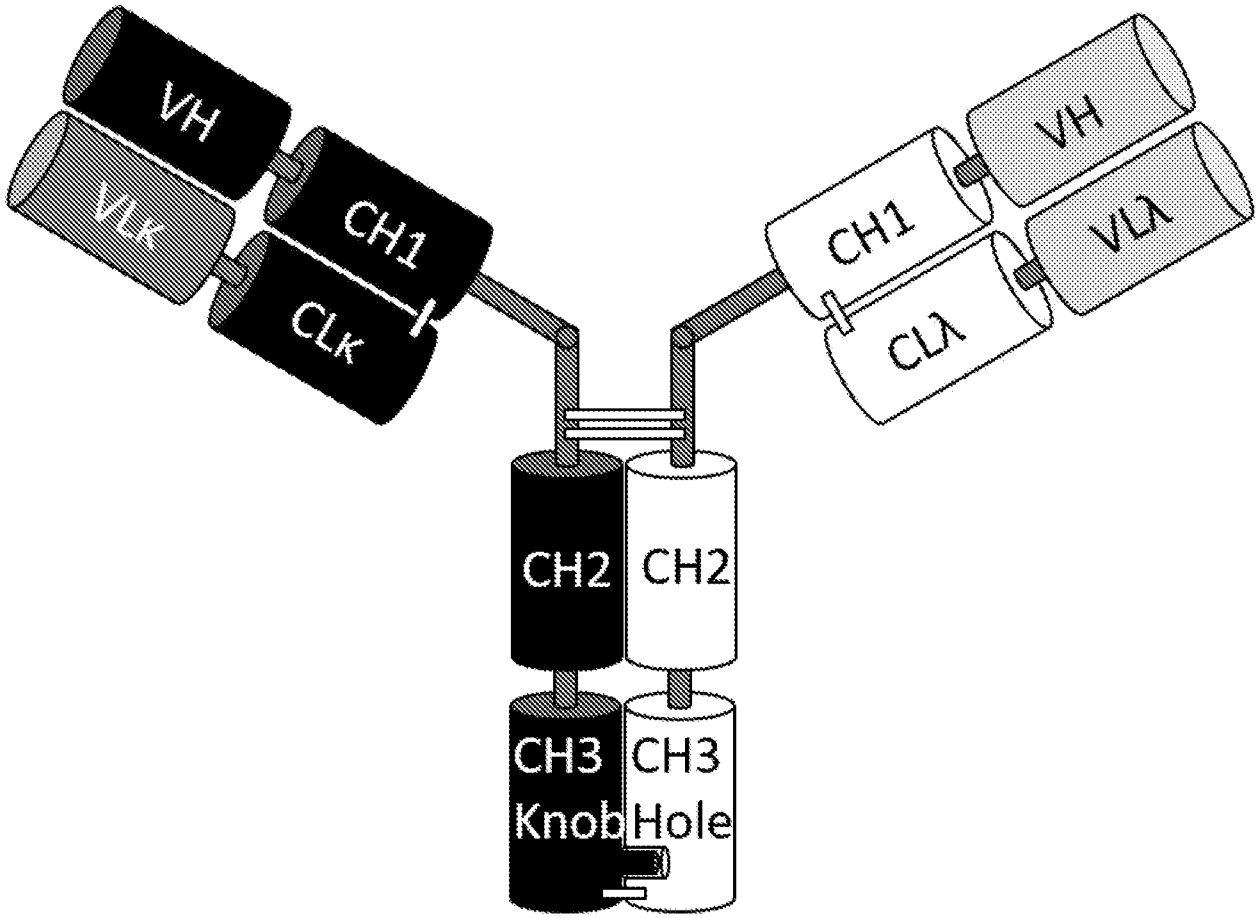


FIG. 5

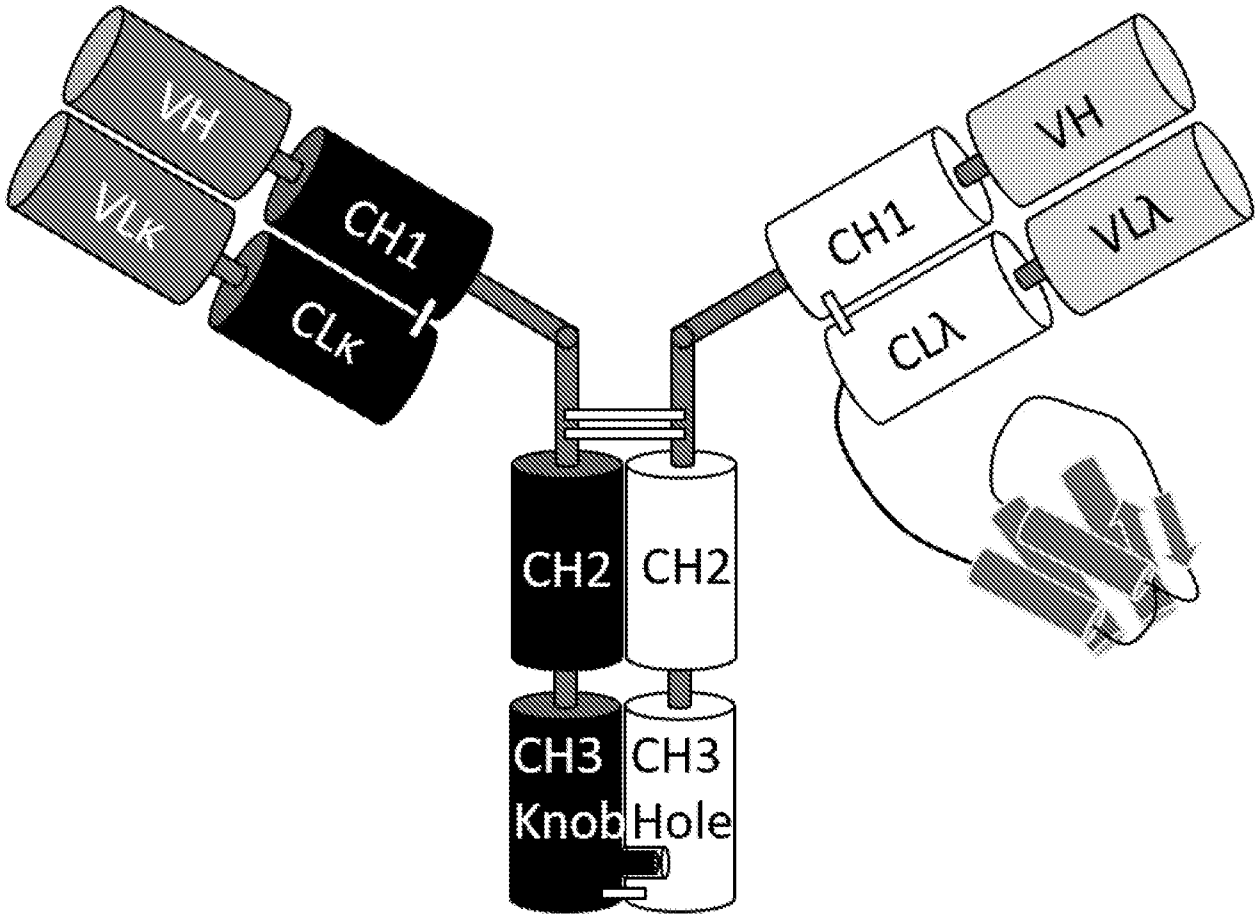


FIG. 6

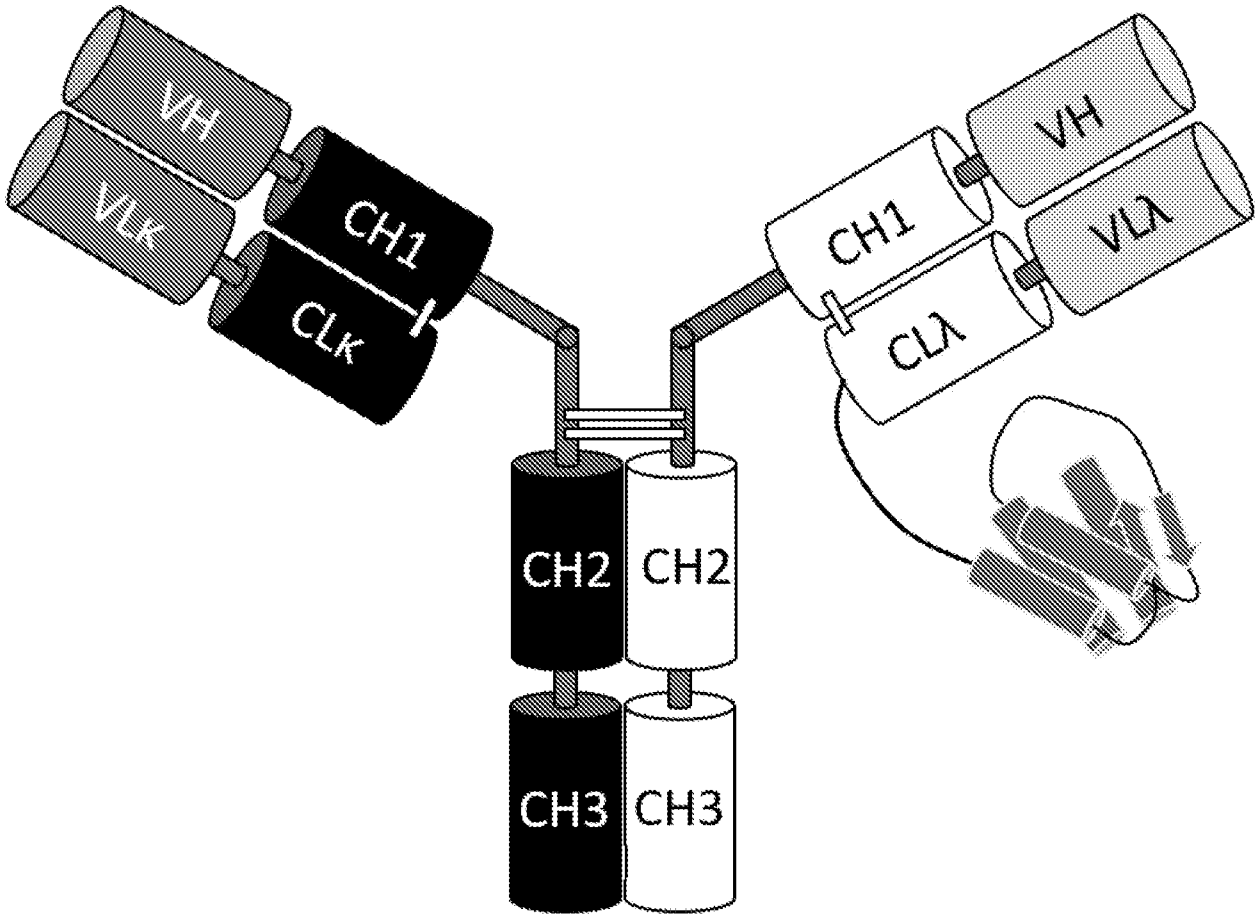


FIG. 7

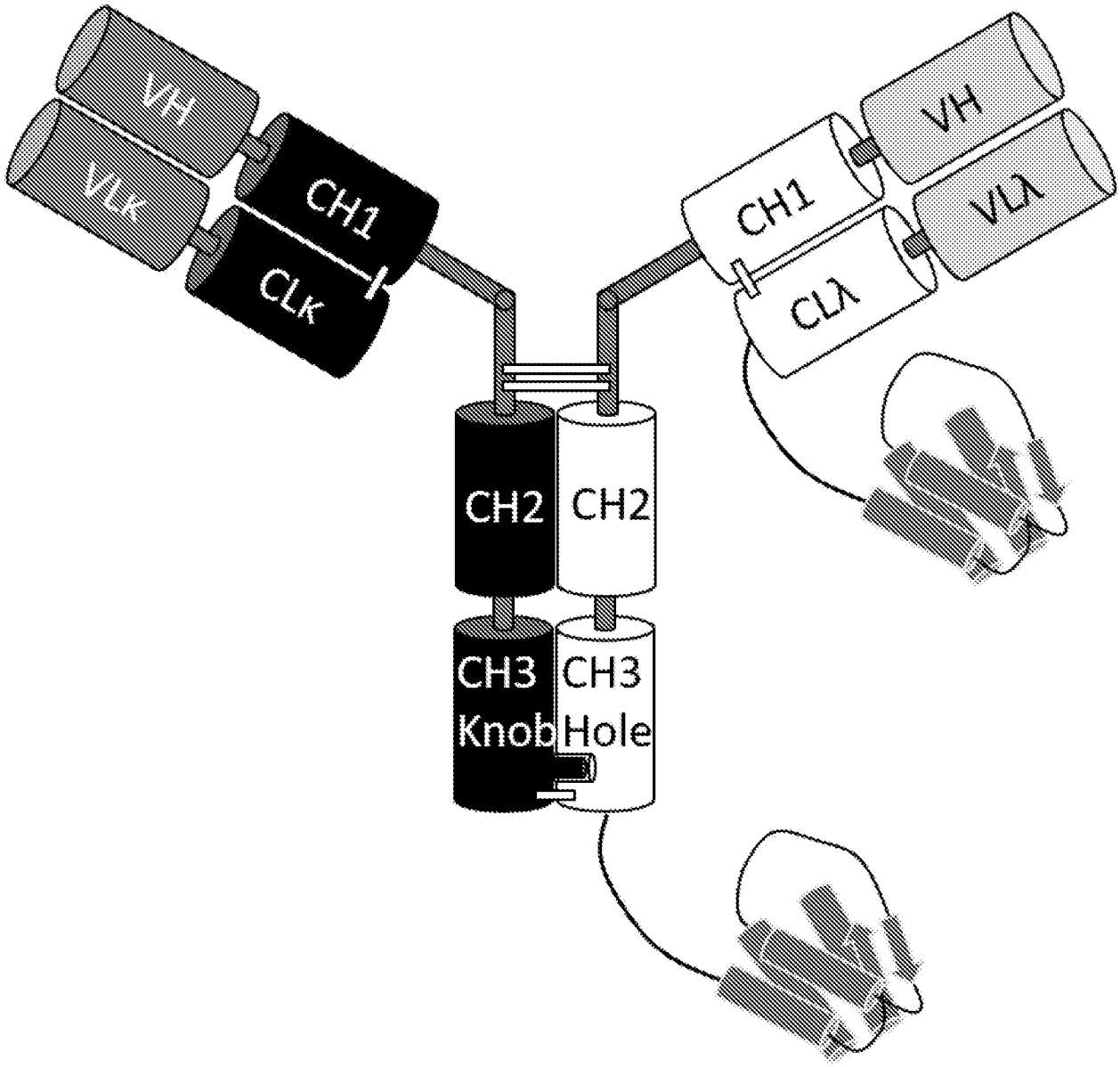


FIG 8

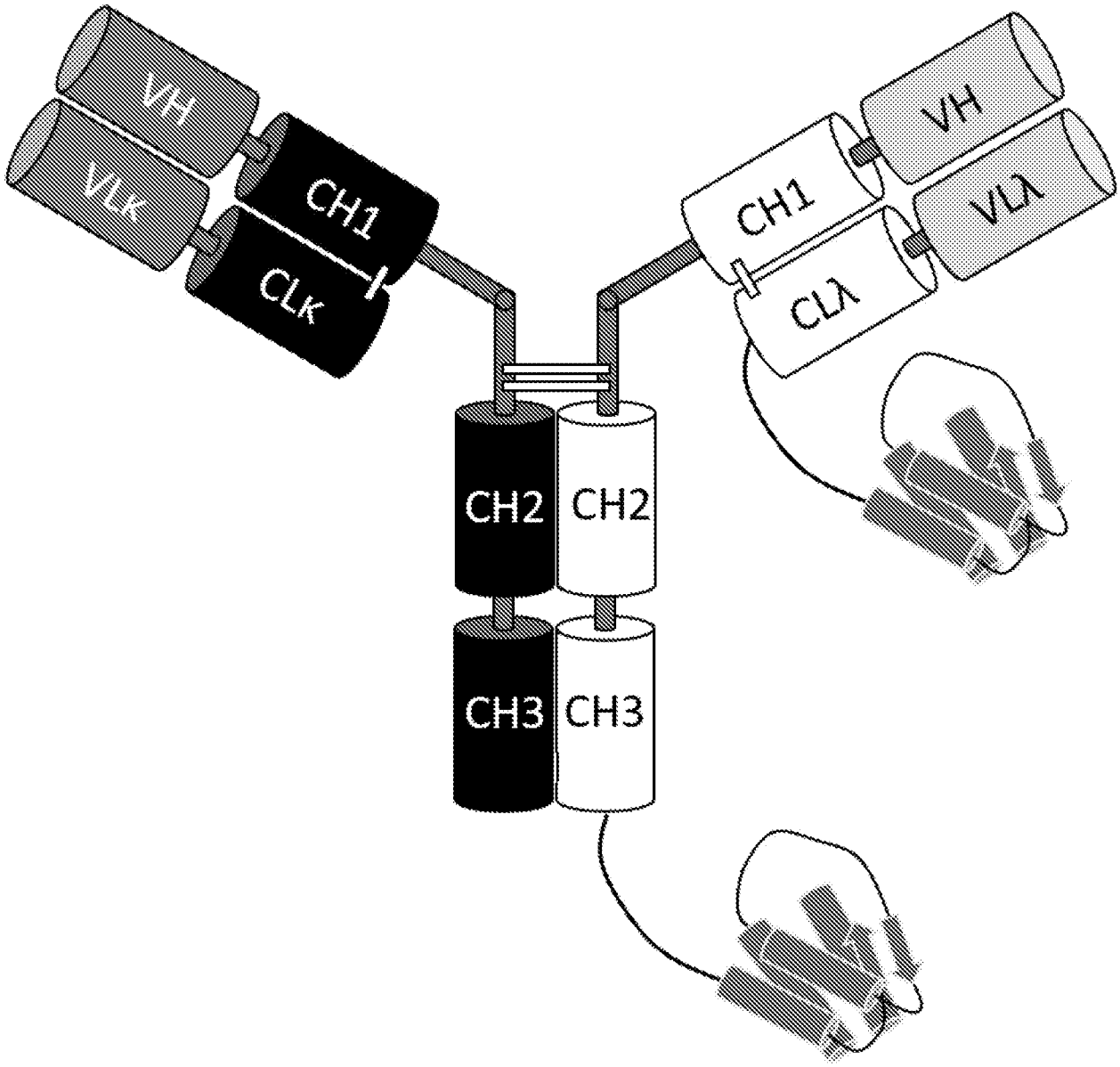


FIG 9

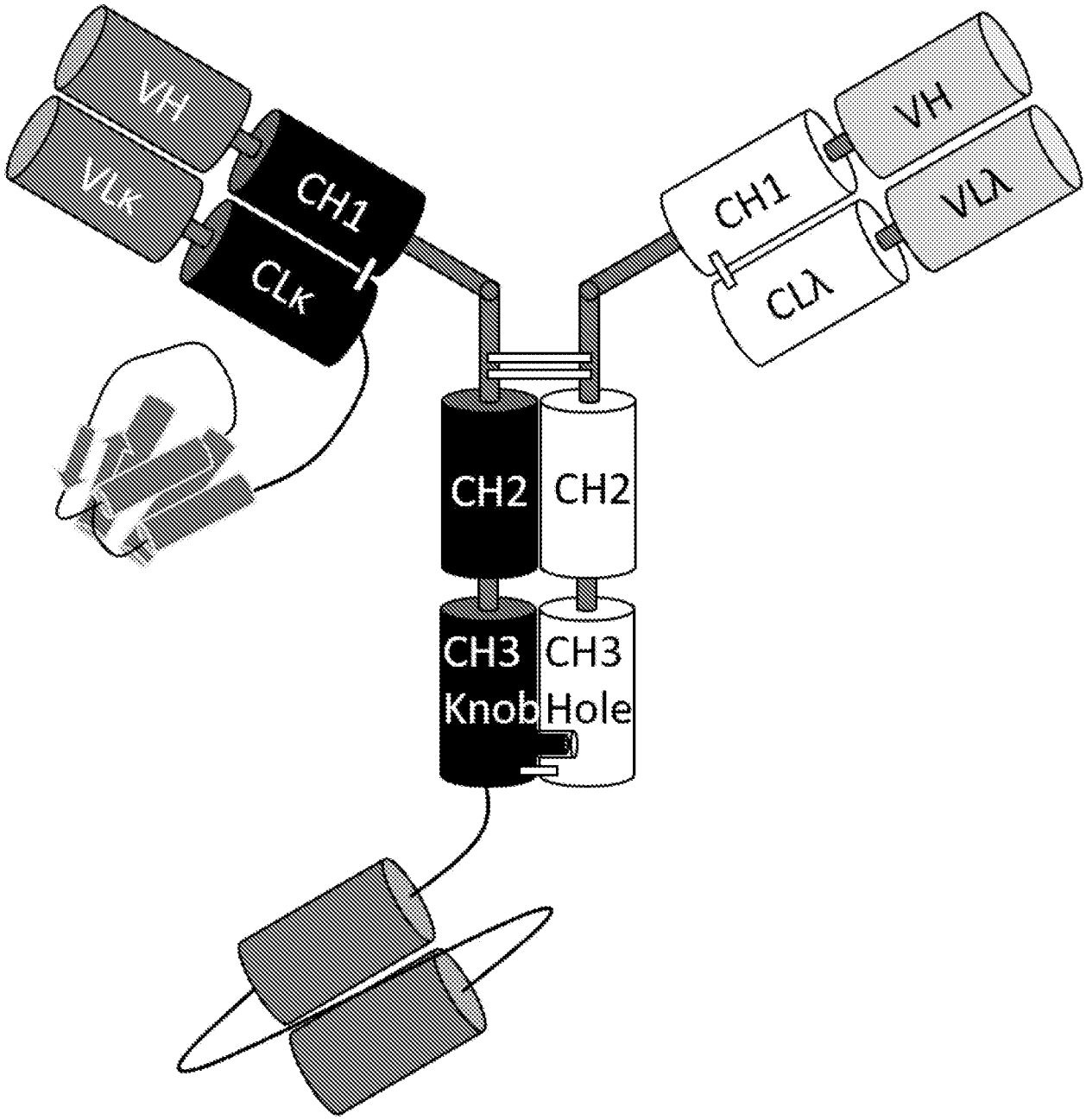
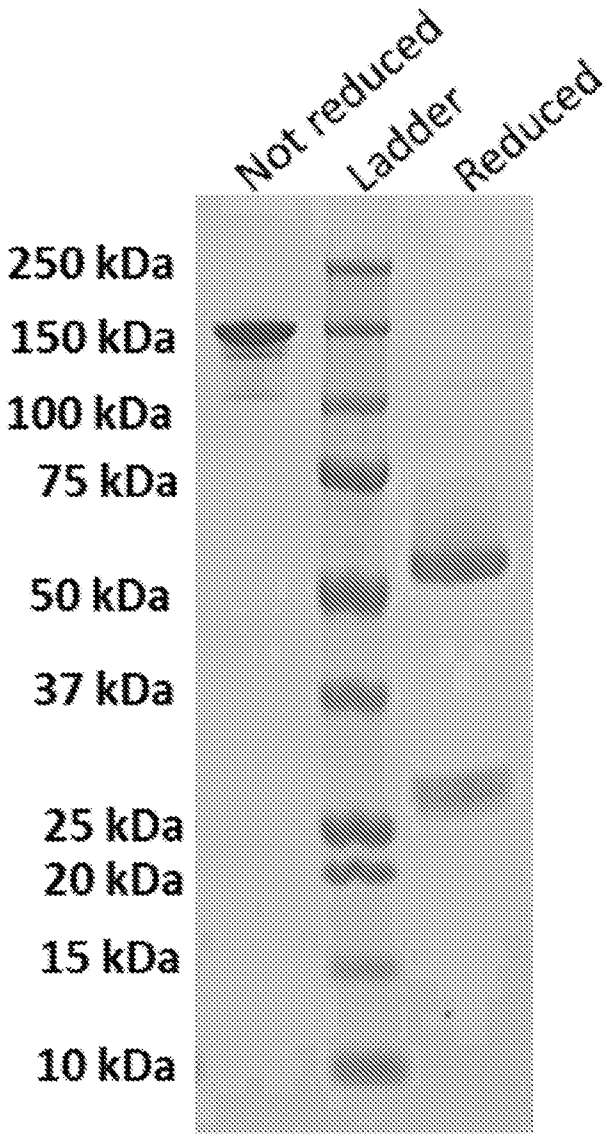
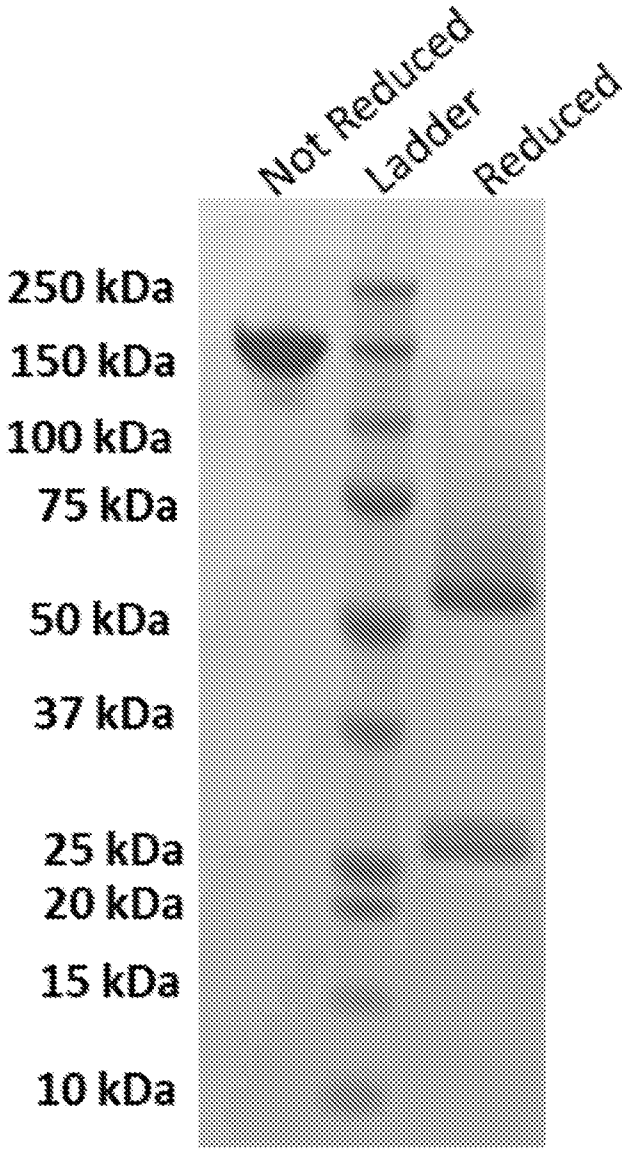


FIG 10



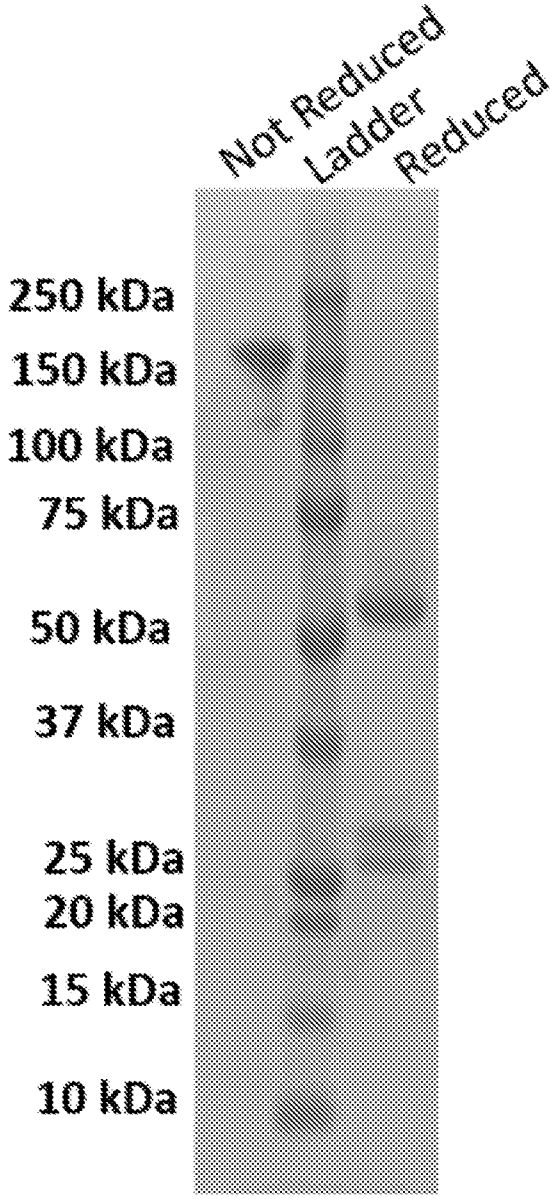
Gel of multispecific molecule 1

FIG. 11



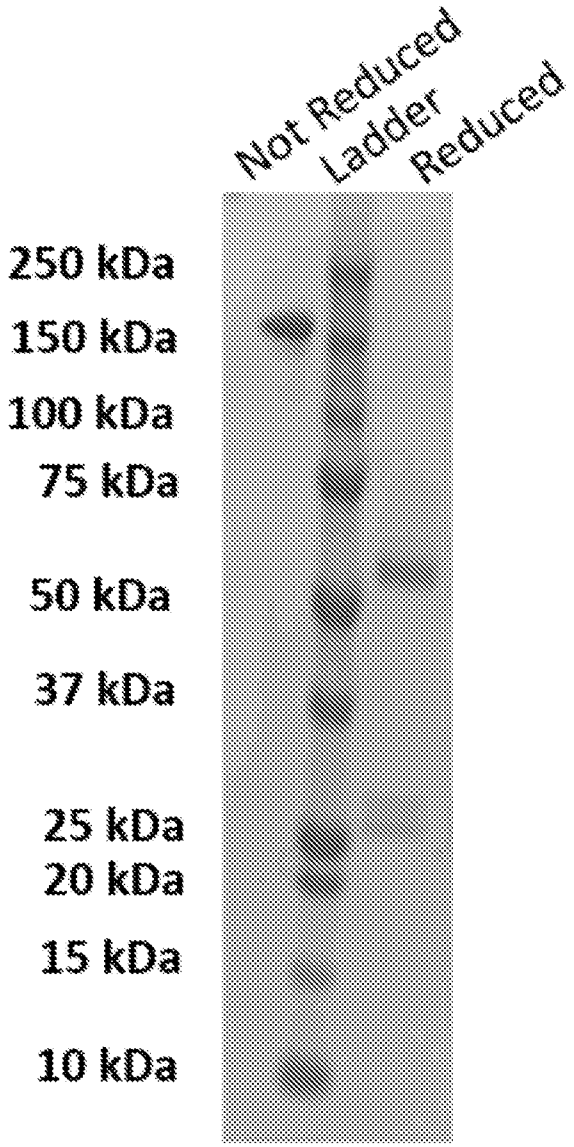
Gel of multispecific molecule 3

FIG. 12



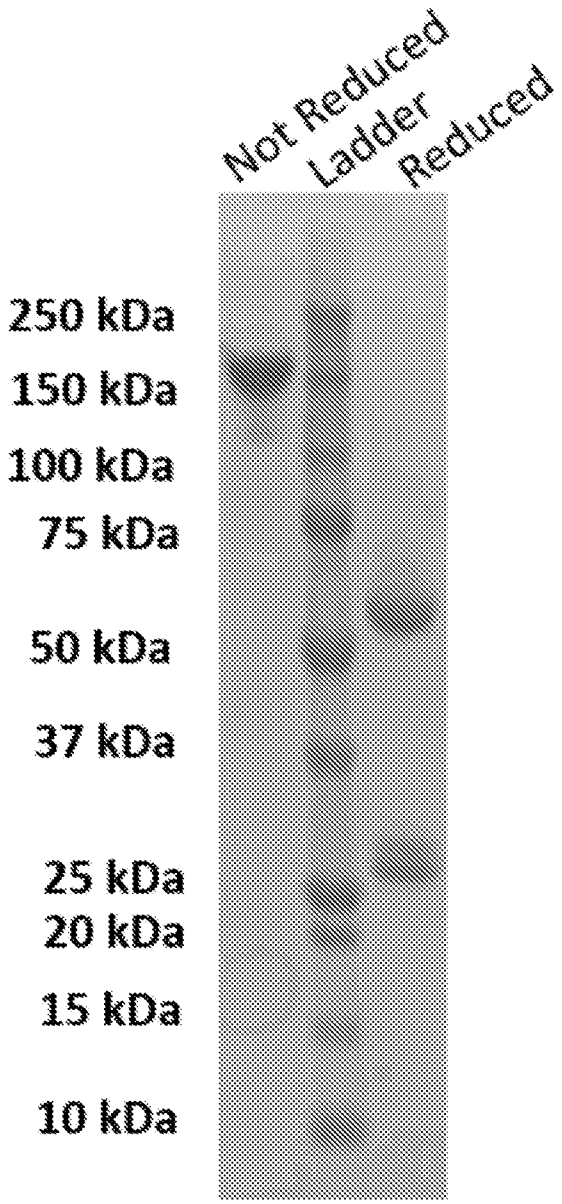
Gel of multispecific molecule 4

FIG. 13



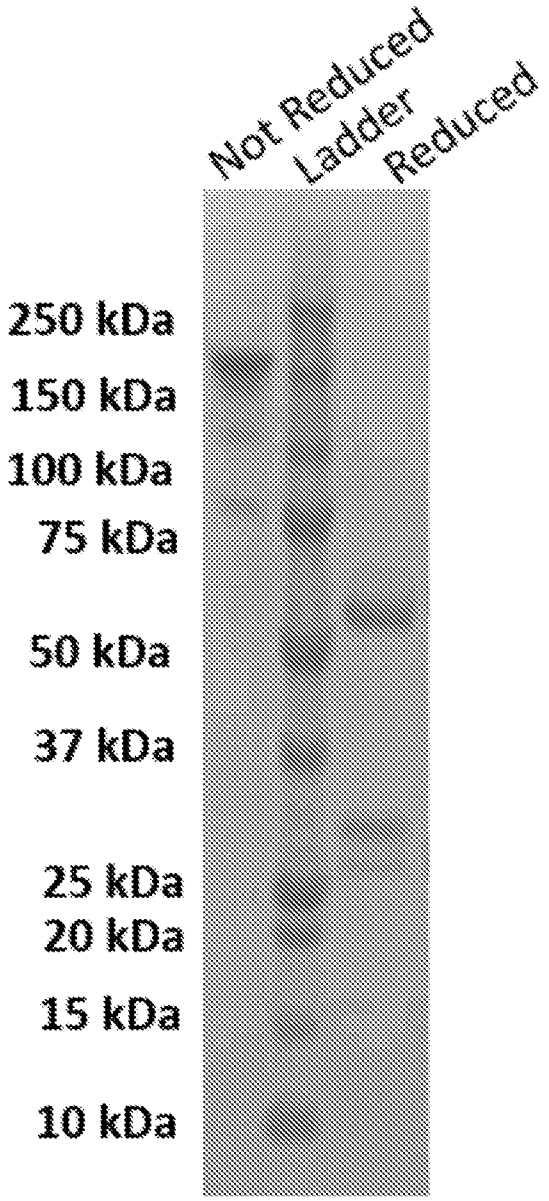
Gel of multispecific molecule 5

FIG. 14



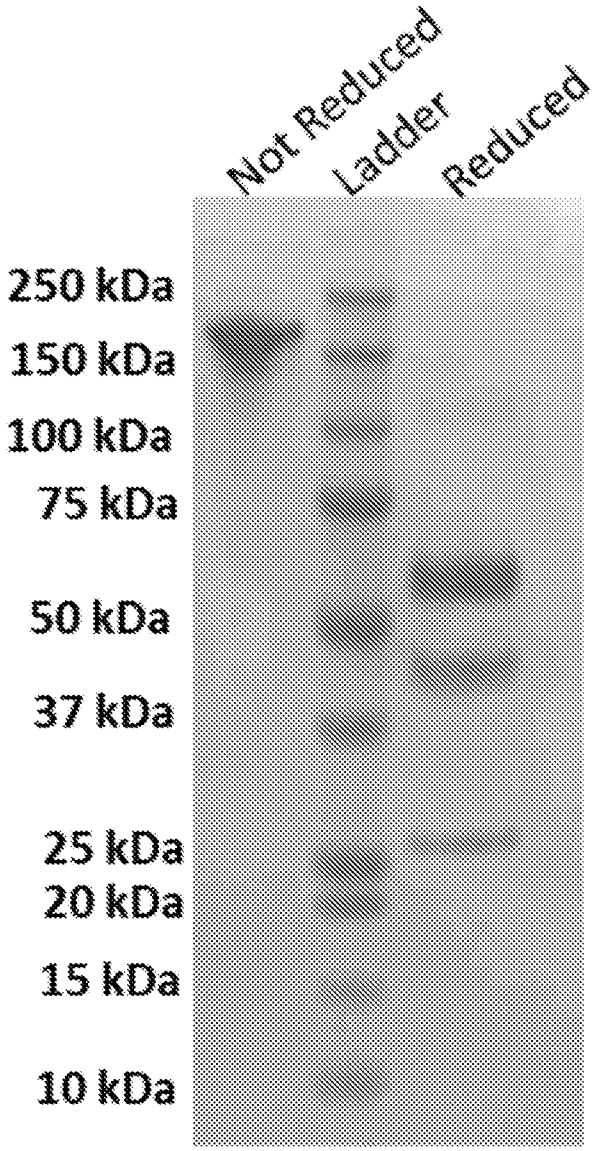
Gel of multispecific molecule 6

FIG. 15



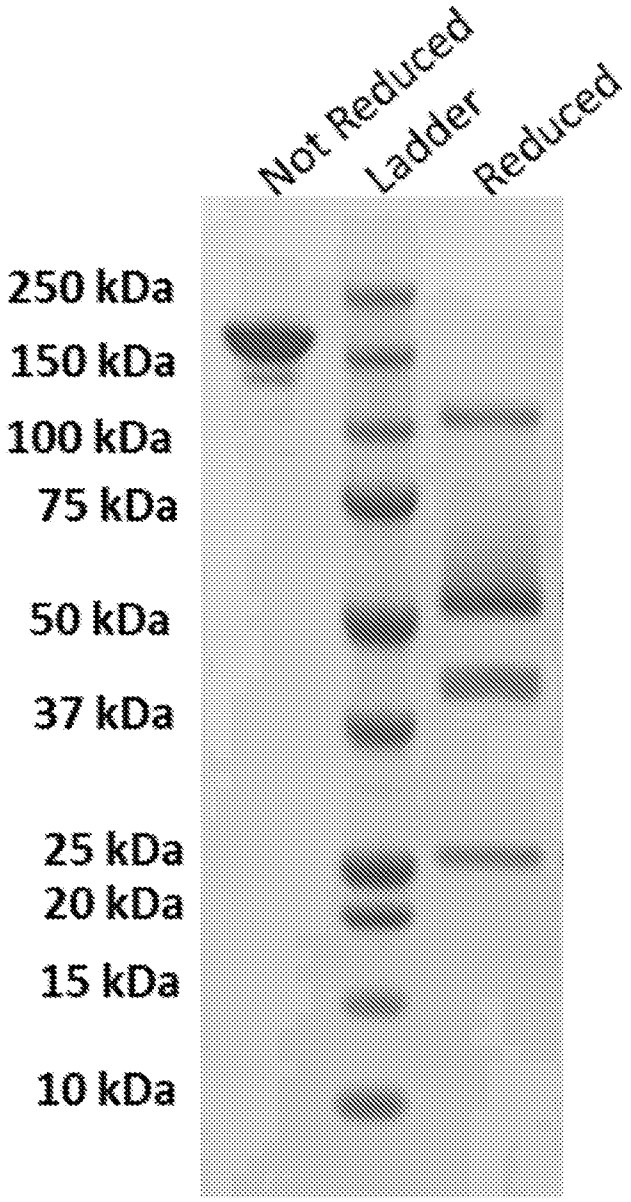
Gel of multispecific molecule 7

FIG. 16



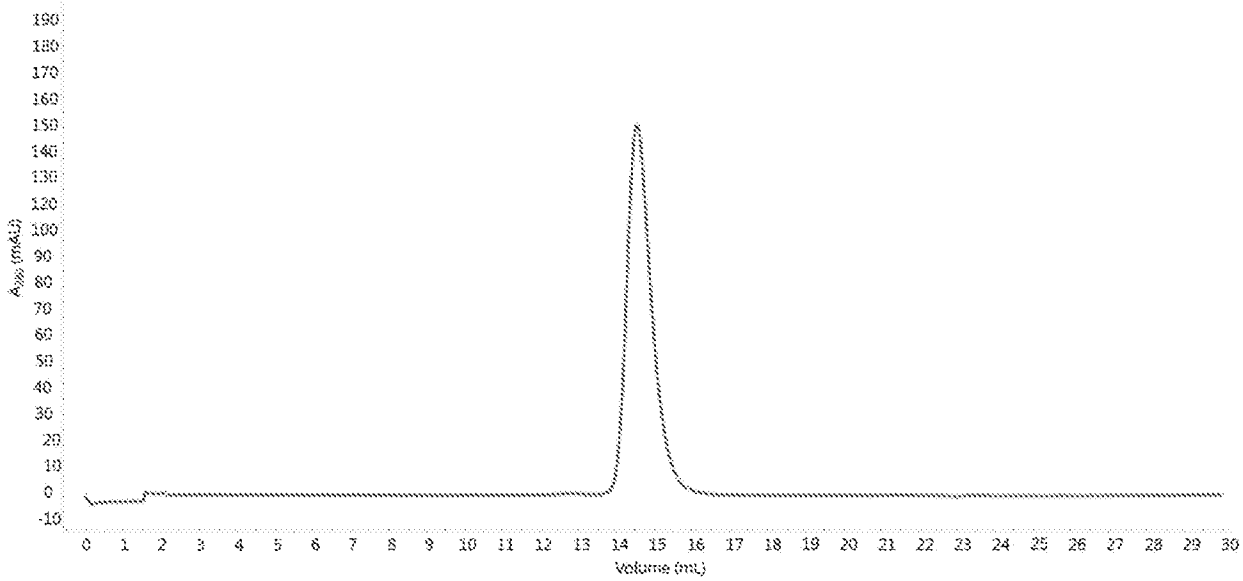
Gel of multispecific molecule 8

FIG. 17



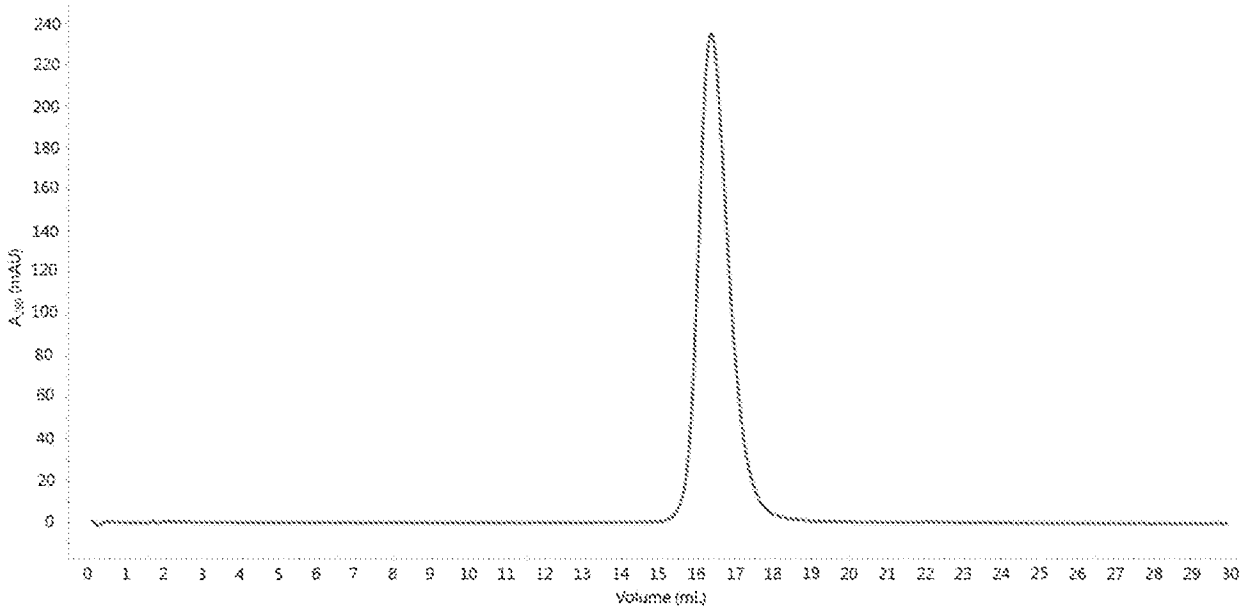
Gel of multispecific molecule 9

FIG. 18



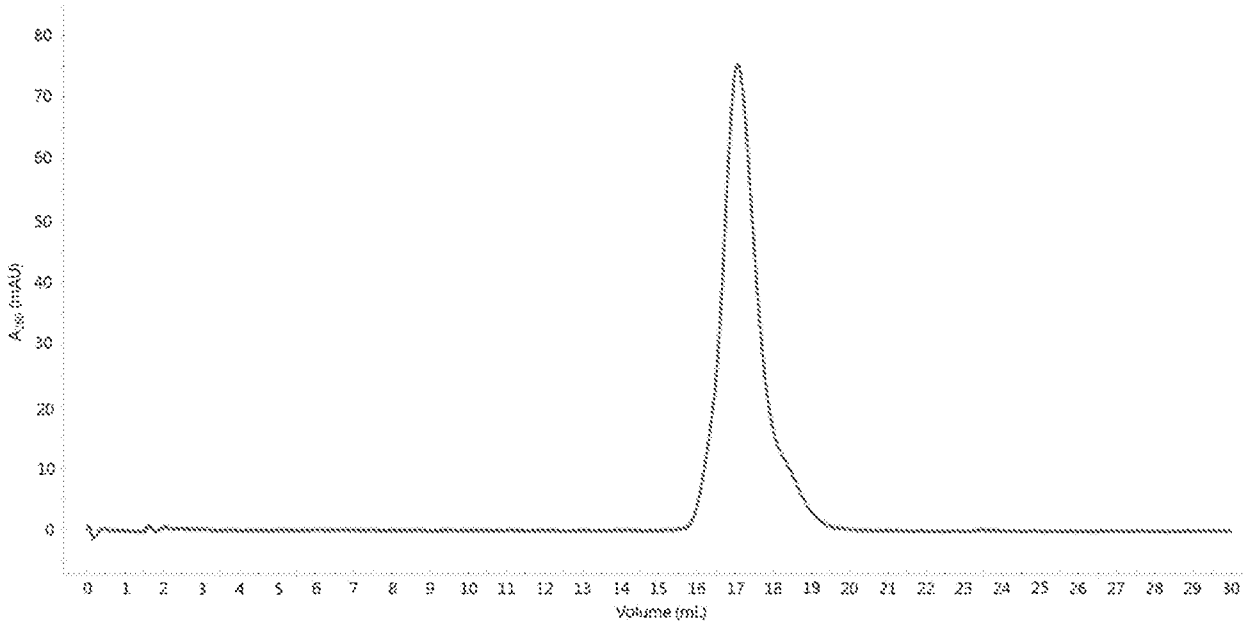
Size exclusion chromatogram of multispecific molecule 1

FIG. 19



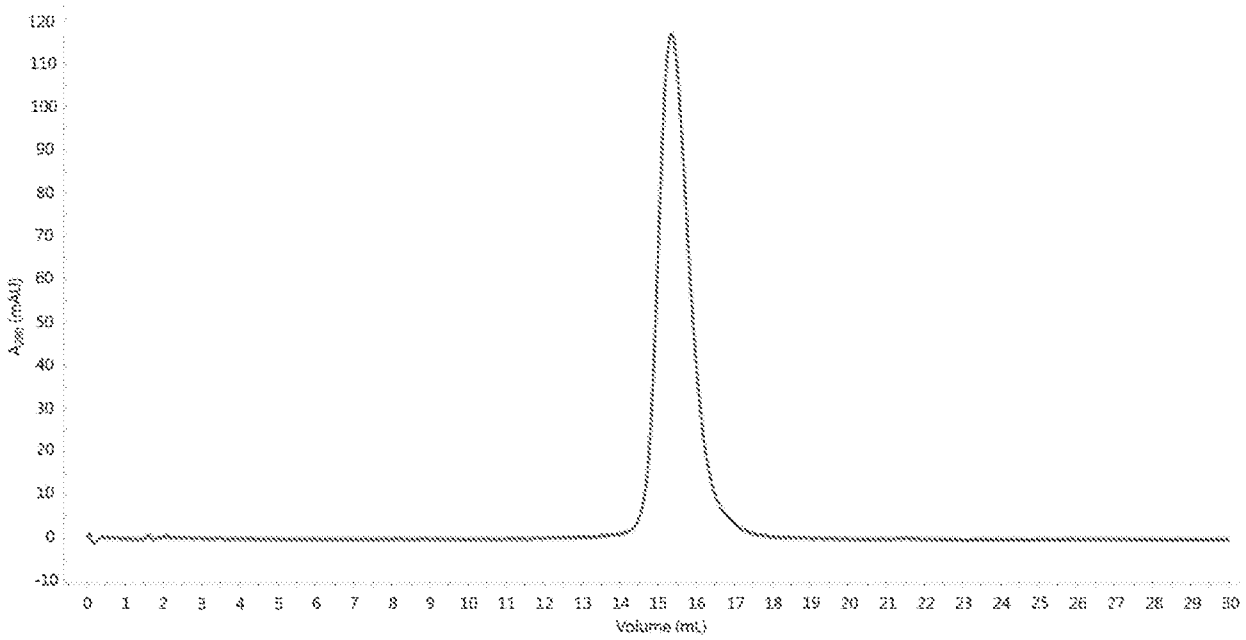
Size exclusion chromatogram of multispecific molecule 3

FIG. 20



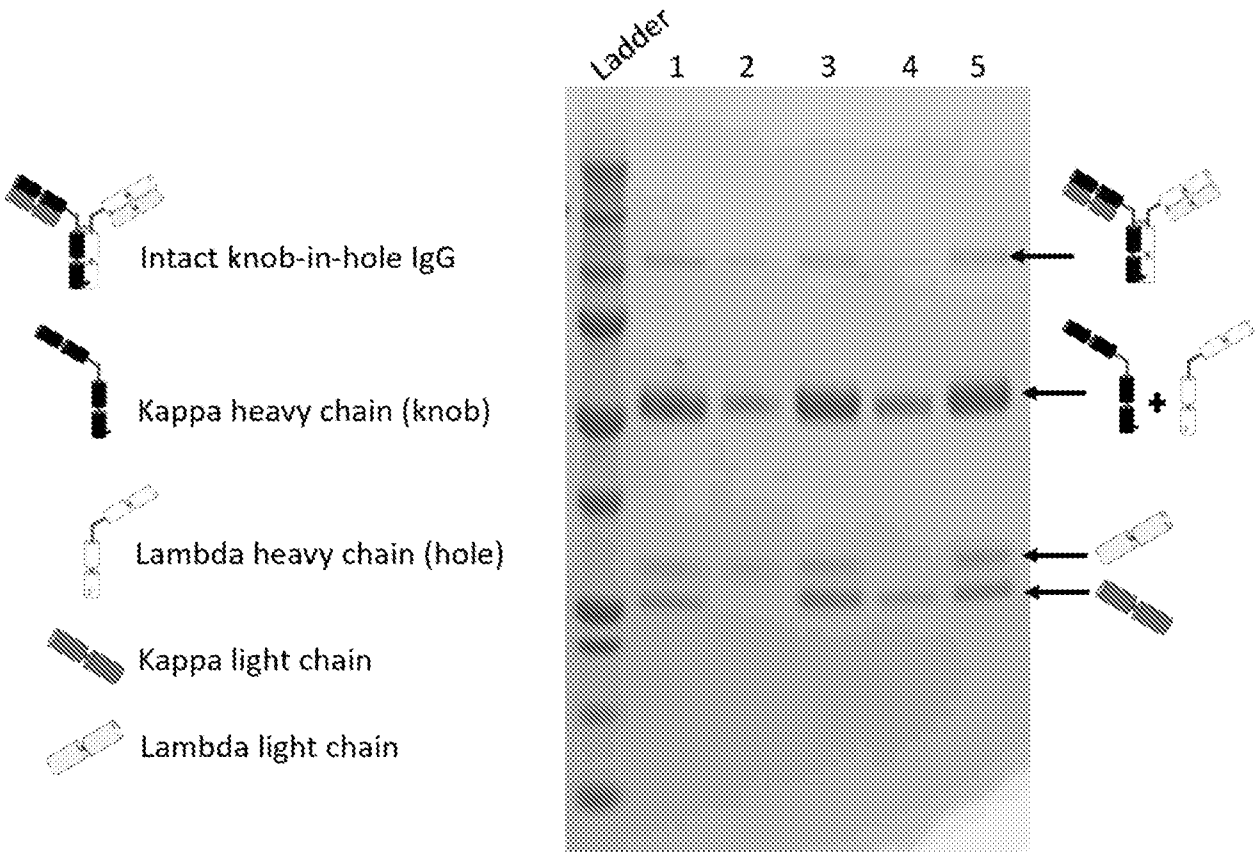
Size exclusion chromatogram of multispecific molecule 8

FIG. 21



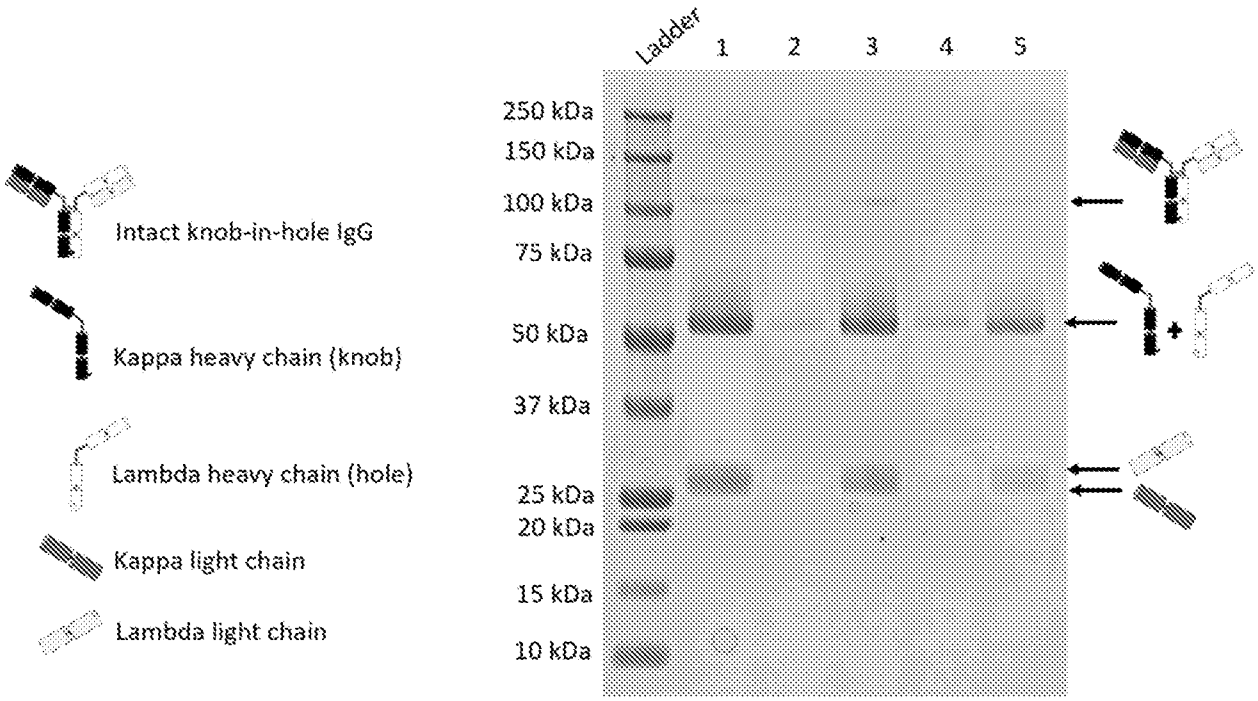
Size exclusion chromatogram of multispecific molecule 9

FIG. 22



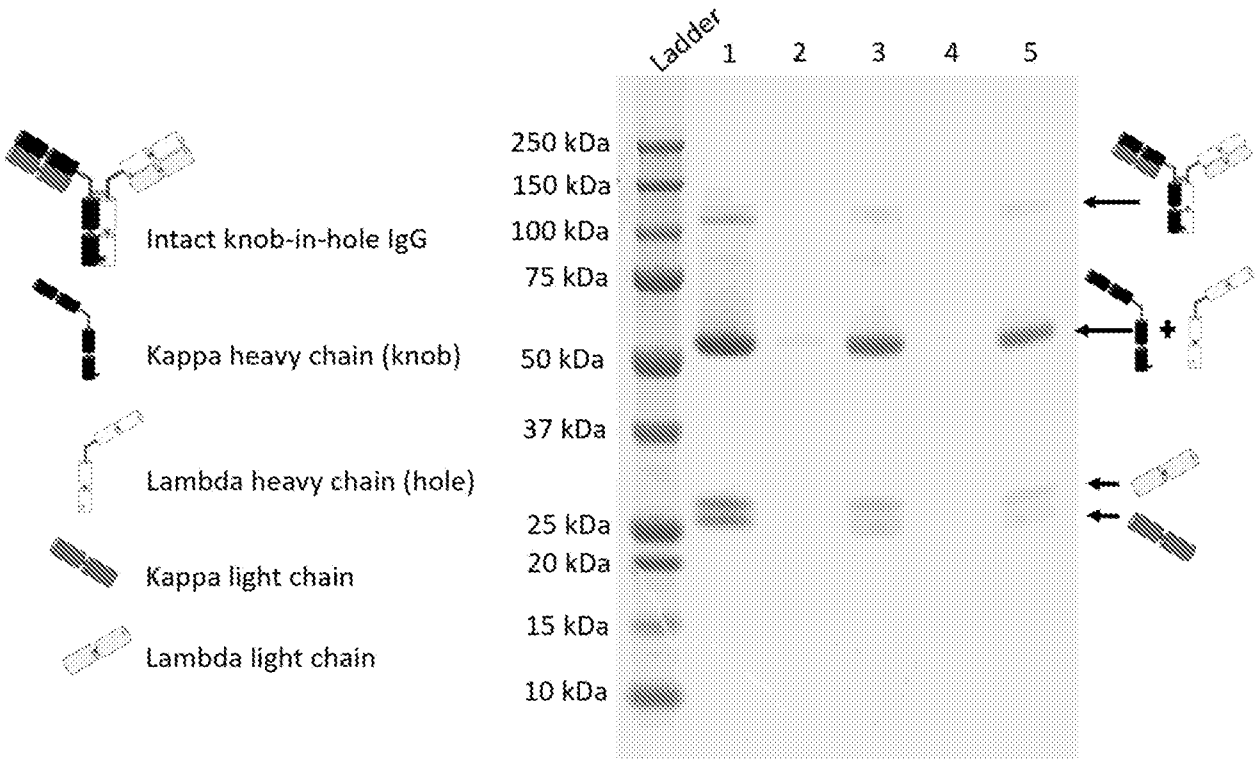
Gel of reduced samples of multispecific molecule 2 following kappa/lambda select analysis

FIG. 23



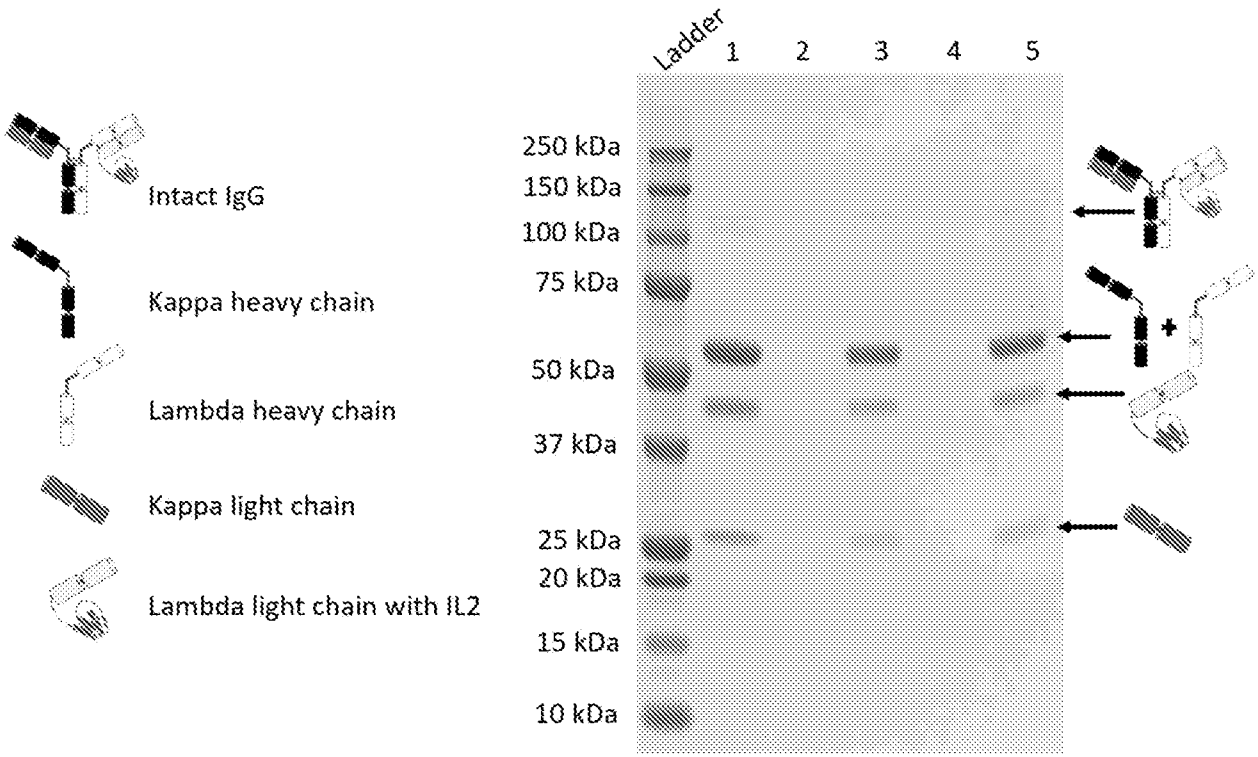
Gel of reduced samples of multispecific molecule 1 following kappa/lambda select analysis

FIG. 24



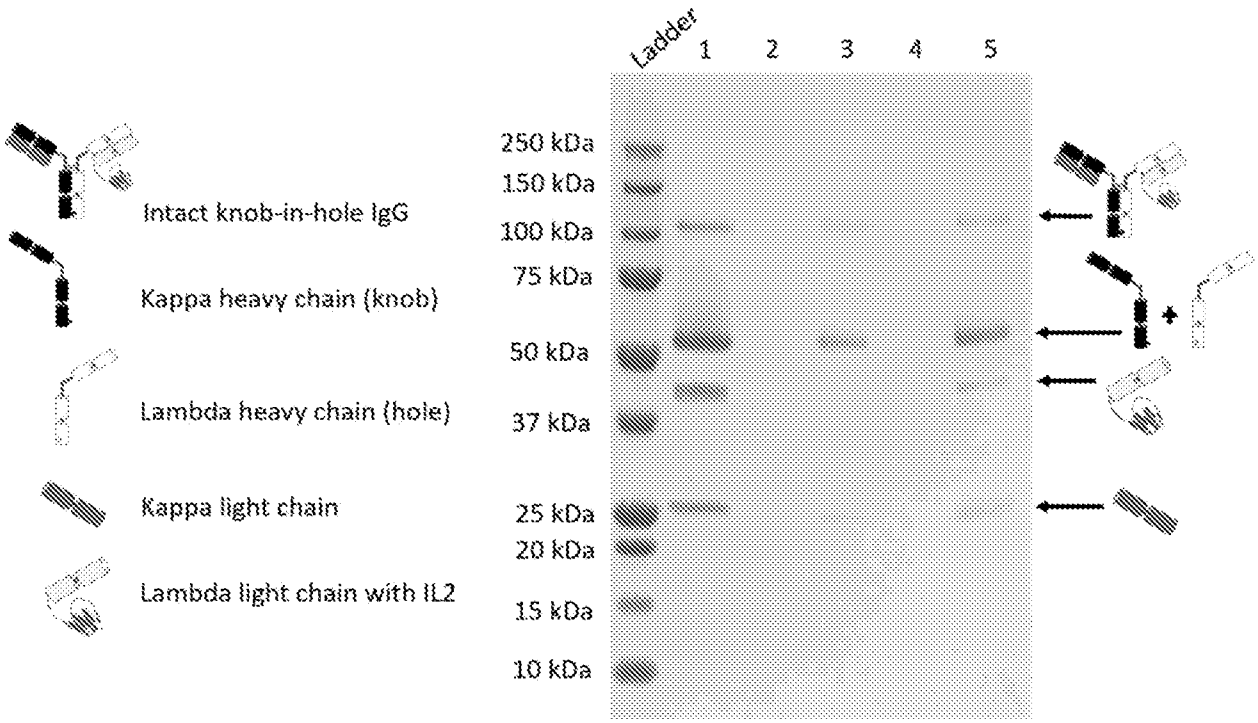
Gel of reduced samples of multispecific molecule 3 following kappa/lambda select analysis

FIG. 25



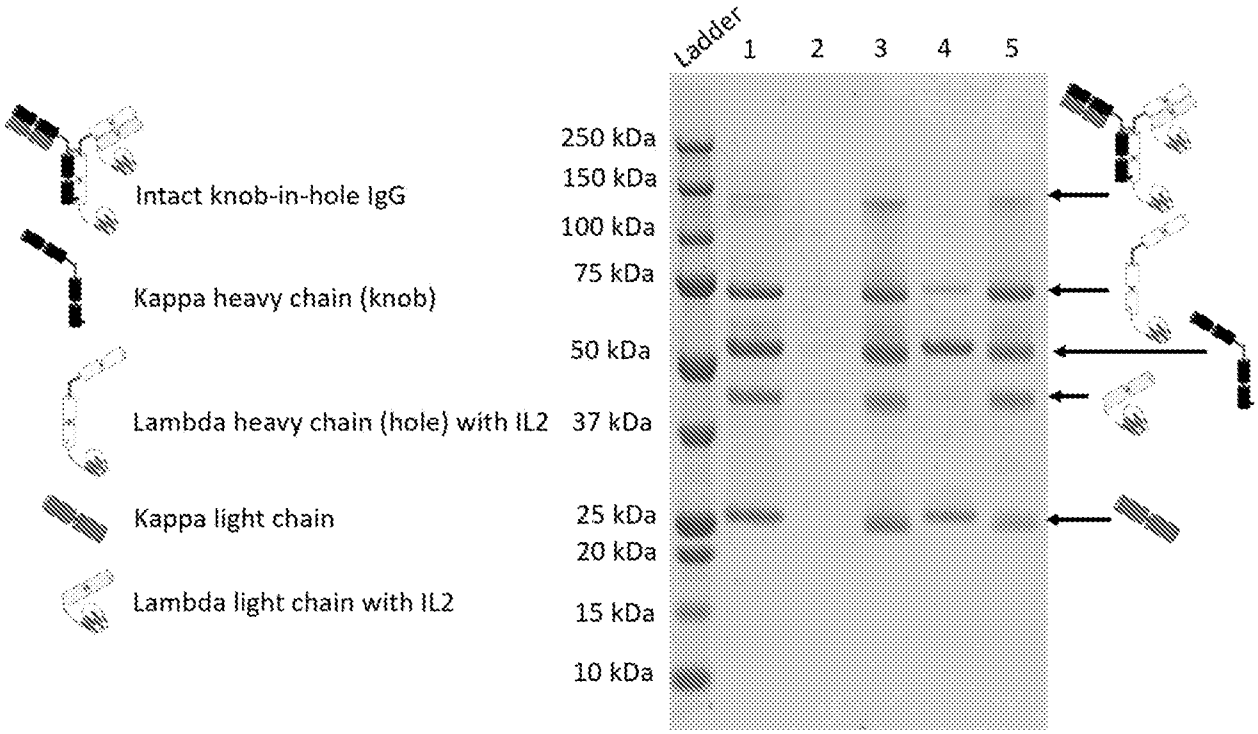
Gel of reduced samples of multispecific molecule 8 following kappa/lambda select analysis

FIG. 26



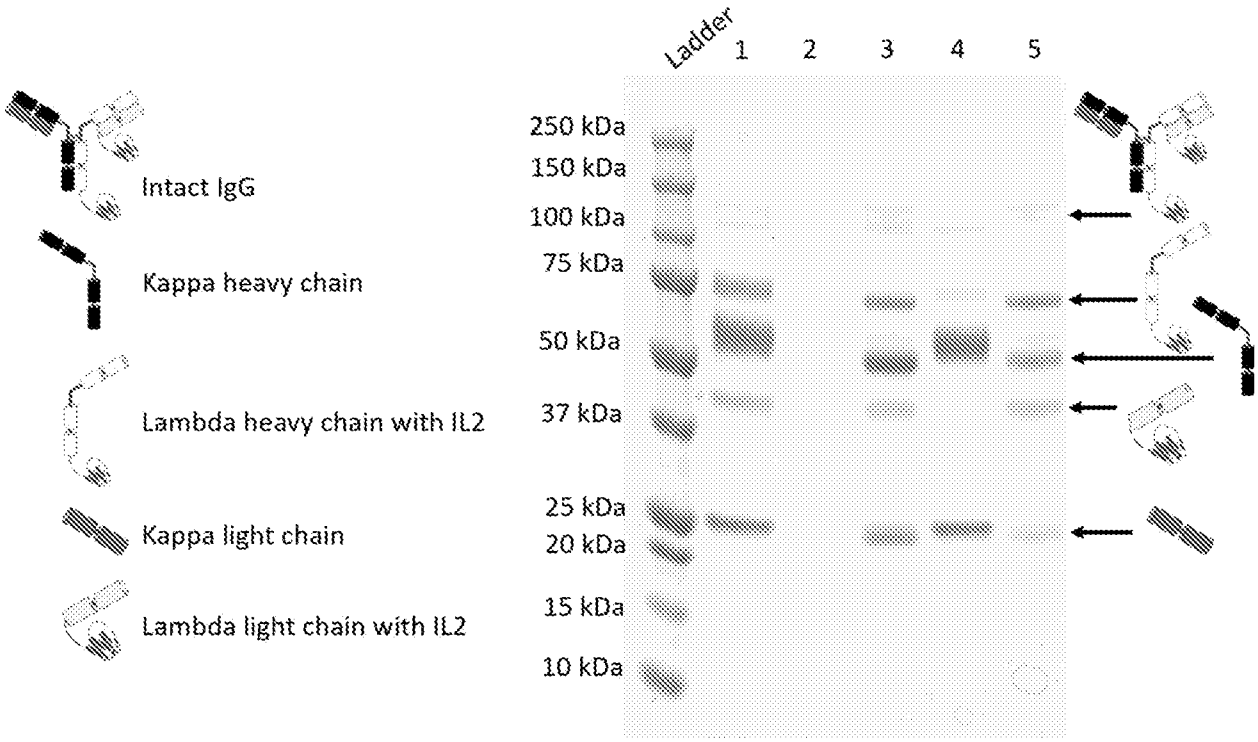
Gel of reduced samples of multispecific molecule 9 following kappa/lambda select analysis

FIG. 27



Gel of reduced samples of multispecific molecule 11 following kappa/lambda select analysis

FIG. 28



Gel of reduced samples of multispecific molecule 10 following kappa/lambda select analysis

FIG. 29

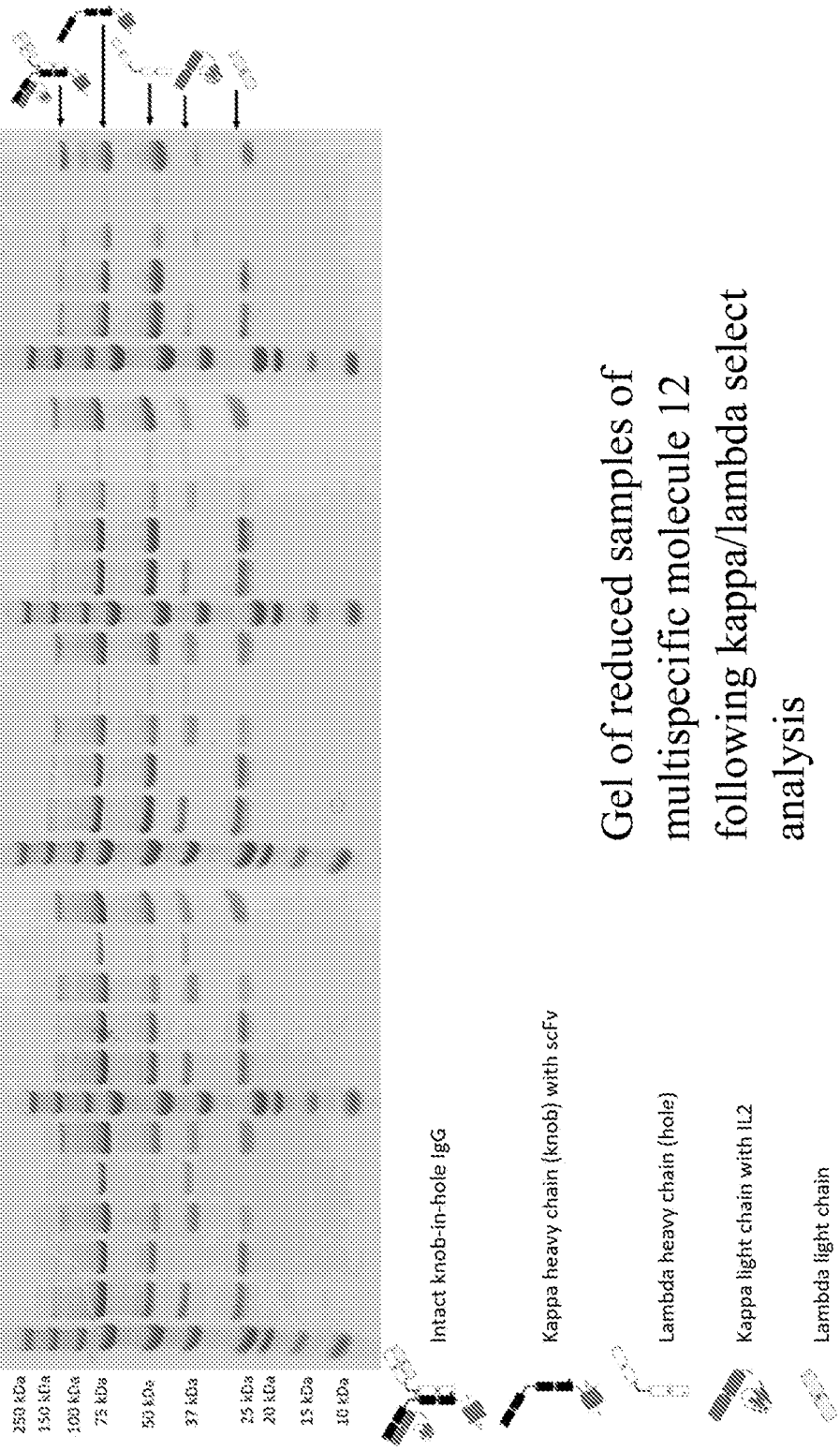
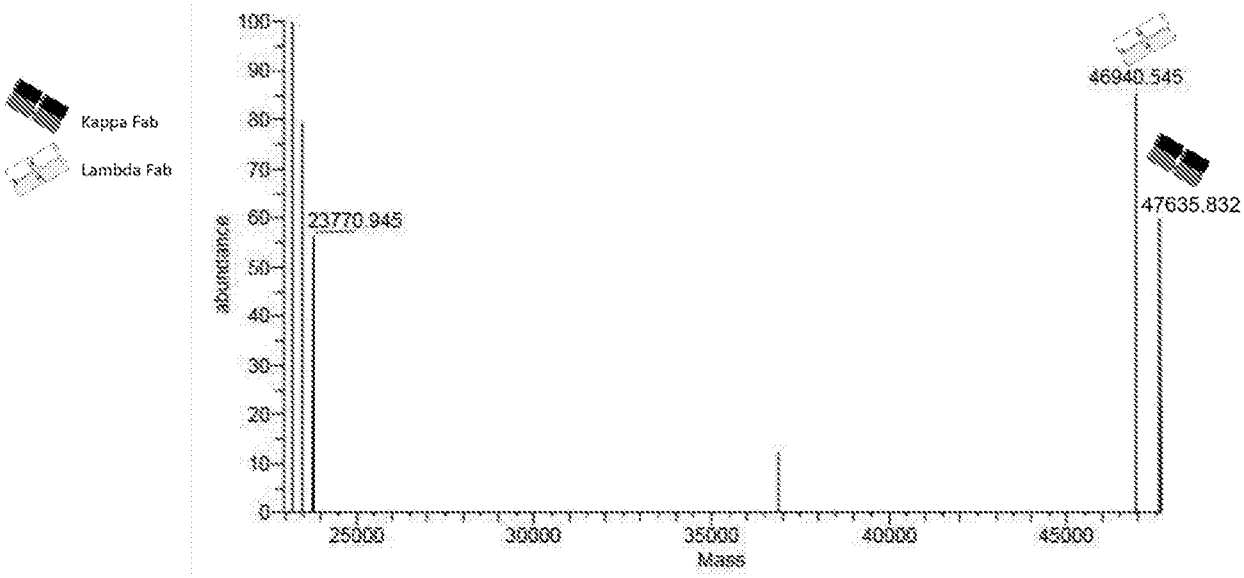
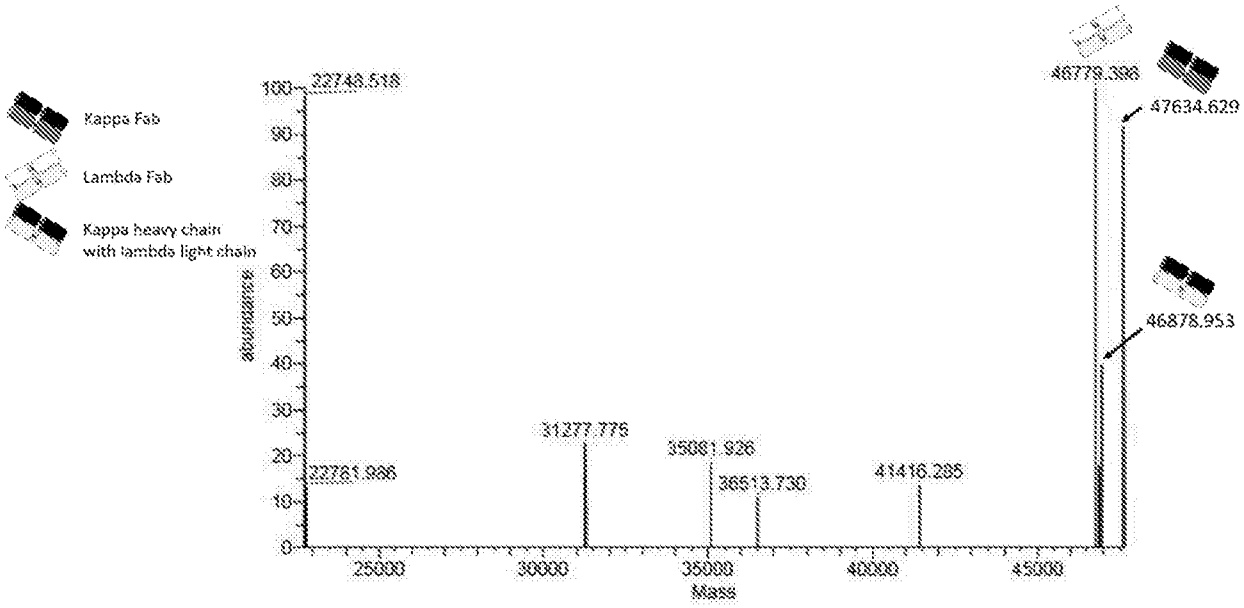

3:1
2:1
1:1
1:2
1:3
Ladder
1
2
3
4
5
250 kDa
150 kDa
100 kDa
75 kDa
50 kDa
37 kDa
25 kDa
20 kDa
15 kDa
10 kDa
Intact knob-in-hole IgG
Kappa heavy chain (knob) with scFv
Lambda heavy chain (hole)
Kappa light chain with IL2
Lambda light chain
Gel of reduced samples of multispecific molecule 12 following kappa/lambda select analysis

FIG. 30



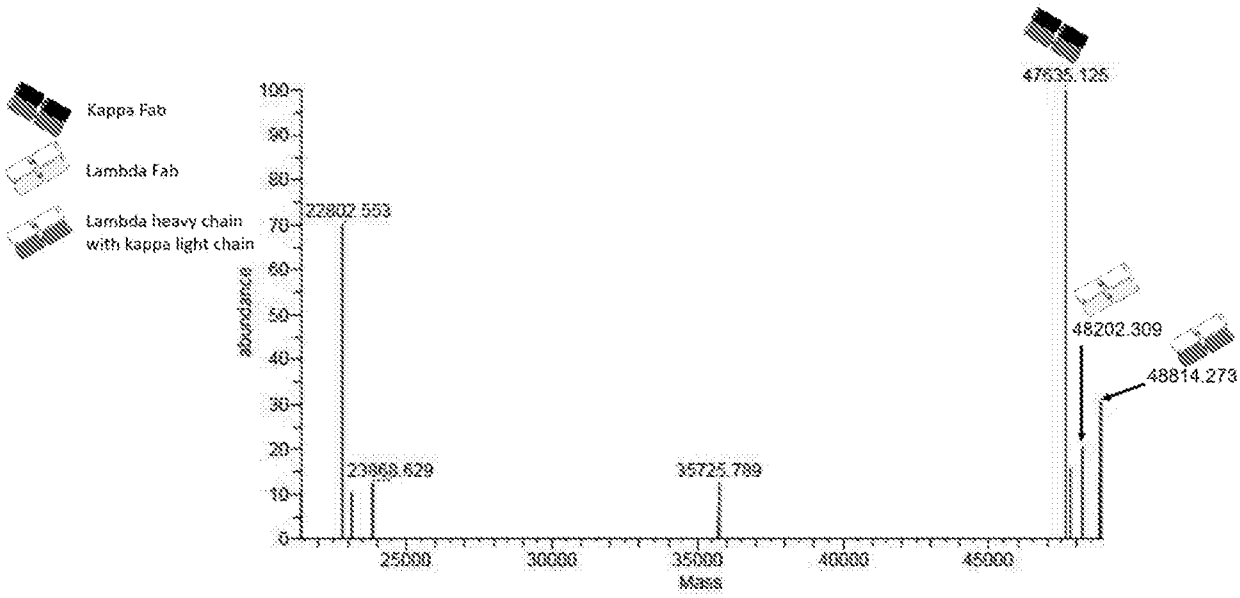
Intact mass spectrometry analysis of papain-cleaved multispecific molecule 3

FIG. 31



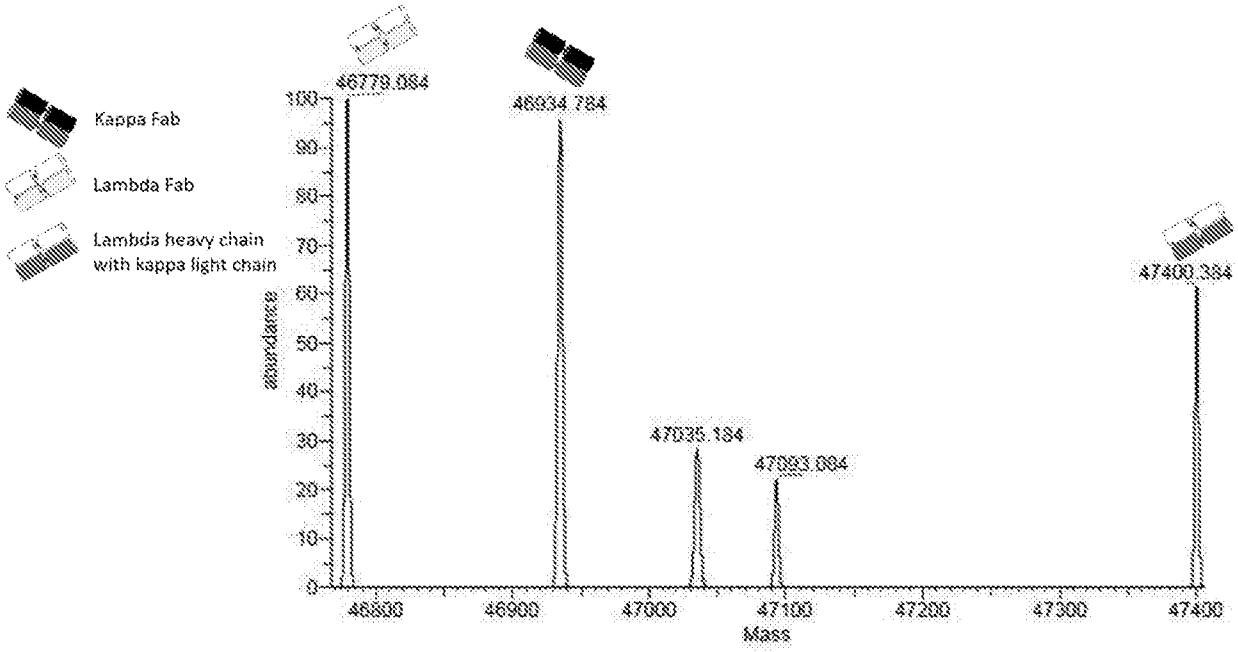
Intact mass spectrometry analysis of papain-cleaved multispecific molecule 4

FIG. 32



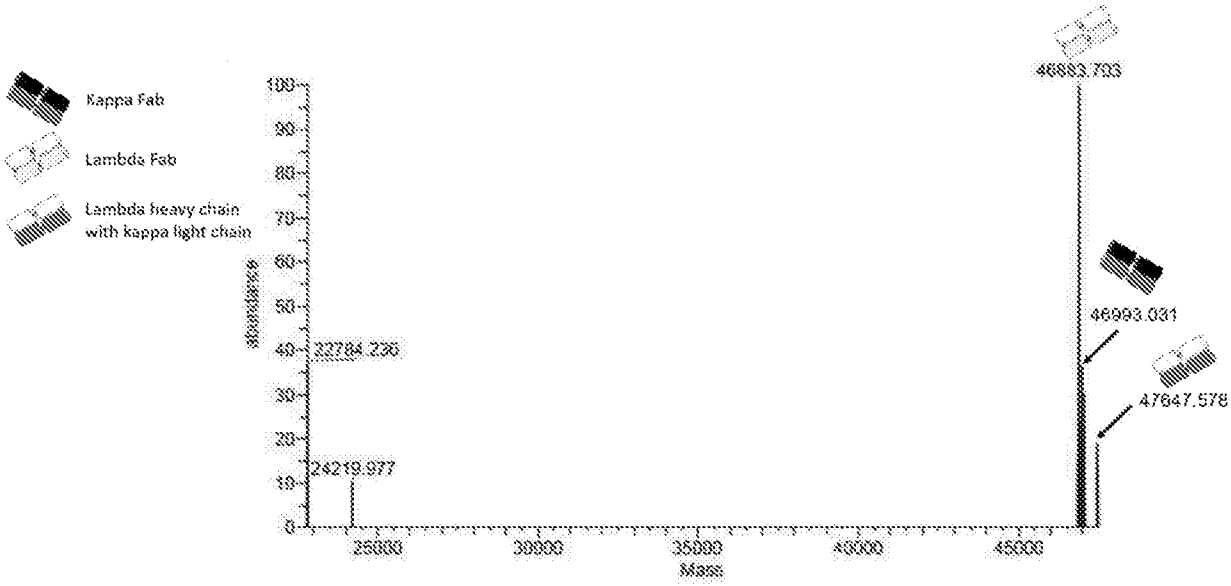
Intact mass spectrometry analysis of papain-cleaved multispecific molecule 5

FIG. 33



Intact mass spectrometry analysis of papain-cleaved multispecific molecule 6

FIG. 34



Intact mass spectrometry analysis of papain-cleaved multispecific molecule 7

FIG. 35

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/053053

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/00 C07K16/46
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FISCHER N ET AL: "Exploiting light chains for the scalable generation and platform purification of native human bispecific IgG", NATURE COMMUNICATIONS,, vol. 6, 12 February 2015 (2015-02-12), pages 6113-1, XP002759070, ISSN: 2041-1723, DOI: 10.1038/NCOMMS7113 [retrieved on 2015-02-12]	53,55, 56,58, 59, 61-121, 123-127
Y	figure all; example all	63-66, 78-80

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 February 2018	27/02/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fellows, Edward

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Eugen Dhimolea ET AL: "World Bispecific Antibody Summit, September 27-28, 2011, Boston, MA", mAbs, 1 January 2012 (2012-01-01), pages 4-13, XP055449732, United States DOI: 10.4161/mabs.4.1.18821 Retrieved from the Internet: URL:http://bispecific.com/wp-content/uploads/sites/90/2015/07/Day-1-1600-Pauline-Malinge-YES.pdf [retrieved on 2018-02-08]	53,55, 56,58, 59, 61-121, 123-127
Y	figure all; example all	63-66, 78-80

X	WO 2012/023053 A2 (NOVIMMUNE SA [CH]; FISCHER NICOLAS [CH]; MAGISTRELLI GIOVANNI [FR]; GU) 23 February 2012 (2012-02-23)	53,55, 56,58, 59, 61-121, 123-127
Y	figure all; example all	63-66, 78-80

A	RAHELEH TOUGHIRI ET AL: "Comparing domain interactions within antibody Fabs with kappa and lambda light chains", MABS, vol. 8, no. 7, 25 July 2016 (2016-07-25), pages 1276-1285, XP055449733, US ISSN: 1942-0862, DOI: 10.1080/19420862.2016.1214785 figure all; example all	53,55, 56,58, 59, 61-121

Y	N. JAYARAM ET AL: "Germline VH/VL pairing in antibodies", PROTEIN ENGINEERING DESIGN AND SELECTION, vol. 25, no. 10, 15 July 2012 (2012-07-15), pages 523-530, XP055216142, ISSN: 1741-0126, DOI: 10.1093/protein/gzs043 figure all; example all	63-66, 78-80

A	WO 2015/052230 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 16 April 2015 (2015-04-16) figure all; example all	53,55, 56,58, 59, 61-121

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/053053

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continuation of Box II.2

Claims Nos.: 1-52, 54, 57, 60, 122(completely); 58, 59, 61-121, 123-127(partially)

The present application comprises 127 claims relating to a plethora of possible multispecific antibodies and variants thereof. According to Rule 6.1(a) PCT, the number of claims shall be reasonable in consideration of the nature of the invention claimed, which is not the case here. The examiner is unable to search said extent of possible antibodies without undue burden.

Furthermore, the application relates to sequence combinations which may or may not generate an antibody with defined technical properties.

In view of the importance of the role played by each single amino acid in the binding of an antibody to its target, especially at the level of its CDRs (see Rudikoff et.al., PNAS 1982, Vol.79, pp. 1979-1983) but also within the framework regions which allow said CDRs to adopt the correct conformation,when presented to the target, a claim to an antibody which is structurally characterised by less than the full sequence of all the CDRs, and their specific order, cannot be seen to sufficiently disclose an antibody with any particular properties. Thus, it is apparent that a search of all possible sequences encompassed in the present claim set would not be useful, since only an antibody defined by at least 6 CDRs (HCDR1-3, LCDR1-3) has any defined technical properties of binding.

In the interests of clarity and for the purposes of a partial search, the applicant was requested to identify the subject-matter to be searched in more detail and was sent an invitation to provide informal clarification dated 22.01.18.

In response to the invitation by the ISA to provide informal clarification regarding the above, the Applicant suggested searching claim 53 as filed in the PCT application. The Examiner has thus limited the scope of the search to the subject-matter of claim 53 and claims dependent thereupon i.e. claims 55, 56 (fully) and claims 58, 59, 61-121, 123-127 (partially) .

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/053053

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012023053 A2	23-02-2012	AU 2011290480 A1	28-02-2013
		CA 2808482 A1	23-02-2012
		CN 103261220 A	21-08-2013
		DK 2606064 T3	20-04-2015
		EP 2606064 A2	26-06-2013
		ES 2537207 T3	03-06-2015
		IL 224674 A	30-04-2017
		JP 5997154 B2	28-09-2016
		JP 2013539461 A	24-10-2013
		JP 2017043611 A	02-03-2017
		MX 338953 B	06-05-2016
		PT 2606064 E	08-06-2015
		RU 2013111533 A	27-09-2014
		US 2012184716 A1	19-07-2012
		US 2014179547 A1	26-06-2014
		WO 2012023053 A2	23-02-2012
WO 2015052230 A1	16-04-2015	CA 2922912 A1	16-04-2015
		CN 105612182 A	25-05-2016
		EP 3055329 A1	17-08-2016
		JP 2016533714 A	04-11-2016
		KR 20160044060 A	22-04-2016
		RU 2016115866 A	16-11-2017
		US 2016319036 A1	03-11-2016
		WO 2015052230 A1	16-04-2015