the IL-15/IL-15Rα complex to NK cells and CD8+ T cells expressing IL-2Rβ and the common gamma chain.

[0005] As potential drugs, both cytokines suffer from a very fast clearance, with half-lives measured in minutes. In addition, IL-15 by itself is less stable due to its preference for the IL-15Rα-associated complex. It has also been shown that recombinantly produced IL15/IL15Rα heterodimer can potently activate T cells. Nevertheless, a short half-life hinders favorable dosing. The present invention solves this problem by providing novel IL15/IL15Rα heterodimer Fc fusion proteins.

SUMMARY

[0005a] In one aspect, the present disclosure refers to a heterodimeric protein comprising: a) a first fusion protein comprising an interleukin-15 (IL-15) protein covalently attached to the N-terminus of a first Fc domain via a first domain linker, wherein the IL-15 protein comprises the amino acid sequence NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIH DTVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS and wherein the first Fc domain comprises the amino acid sequence EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFN WYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK; and

b) a second fusion protein comprising an IL-15 receptor alpha (IL-15Rα) protein covalently attached to the N-terminus of a second Fc domain via a second domain linker, wherein the IL-15Rα protein comprises the amino acid sequence ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPS LKCIR and wherein the second Fc domain comprises the amino acid sequence EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK.

[0005b] In another aspect, the present disclosure refers to a heterodimeric protein comprising a first fusion protein and a second fusion protein, wherein the first fusion protein comprises the amino acid sequence NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHD TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSEPKSS DKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDG VEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK and the second fusion protein comprises the amino acid sequence ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSL KCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK.

[0005c] In another aspect, the present disclosure refers to a heterodimeric protein comprising: a) a first fusion protein comprising an interleukin-15 (IL-15) protein covalently attached to the N-terminus of a first Fc domain via a first domain linker, wherein the IL-15 protein comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHD TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS and wherein the first Fc domain comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNW YVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK; and

b) a second fusion protein comprising an IL-15 receptor alpha (IL-15Rα) protein covalently attached to the N-terminus of a second Fc domain via a second domain linker, wherein the IL-15Rα protein comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR and wherein the second Fc domain comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK.

[0005c] In another aspect, the present disclosure refers to a heterodimeric protein comprising a first fusion protein and a second fusion protein, wherein the first fusion protein comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK and the second fusion protein comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK.

[0005d] In another aspect, the present disclosure refers to a nucleic acid composition comprising: a) a first nucleic acid encoding the first fusion protein as disclosed herein; and b) a second nucleic acid encoding the second fusion protein as disclosed herein.

[0005e] In another aspect, the present disclosure refers to an expression vector composition comprising: a) a first expression vector comprising the first nucleic acid as disclosed herein; and b) a second expression vector comprising the second nucleic acid as disclosed herein.

[0005f] In another aspect, the present disclosure refers to a host cell comprising the expression vector composition as disclosed herein.

[0005g] In another aspect, the present disclosure refers to a method of producing a heterodimeric protein comprising culturing the host cell as disclosed herein under suitable conditions wherein said heterodimeric protein is expressed, and recovering said protein.

[0005h] In another aspect, the present disclosure refers to a composition comprising a human interleukin 15 (IL-15) variant comprising the amino acid sequence NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHD TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS.

[0005i] In another aspect, the present disclosure refers to a nucleic acid encoding the composition comprising the IL-15 variant as disclosed herein.

[0005j] In another aspect, the present disclosure refers to an expression vector comprising the nucleic acid as disclosed herein.

[0005k] In another aspect, the present disclosure refers to a host cell comprising the nucleic acid as disclosed herein or the expression vector as disclosed herein.

[0006] Accordingly, in one ~~aspect~~ example the present disclosure refers to a heterodimeric protein comprising a) a first fusion protein comprising a first protein domain and a first Fc domain, wherein the first protein domain is covalently attached to the N-terminus of the first Fc domain using a first domain linker; b) a second fusion protein comprising a second protein domain and a second Fc domain, wherein the second protein domain is covalently attached to the N-terminus of the Fc domain using a seconddomain linker; wherein the first and the second Fc domains have a set of amino acid substitutions selected from the group consisting of S267K/L368D/K370S : S267K/S364K/E357Q; S364K/E357Q : L368D/K370S; L368D/K370S : S364K; L368E/K370S : S364K; T411E/K360E/Q362E : D401K; L368D/K370S : S364K/E357L and K370S : S364K/E357Q, according to EU numbering and wherein the first protein domain comprises an IL15 protein and the second protein domain comprises an IL15Rα protein, wherein said IL-15 protein comprises one or more amino acid substitutions selected from the group consisting of N1D, N4D, D8N, D30N, D61N, E64Q, N65D, and Q108E. In some examples, the first protein domain is covalently attached to the N-terminus of the first Fc domain directly and without using the first domain linker and/or the second protein domain is covalently attached to the N-terminus of the second Fc domain directly and without using the second domain linker.

[0007] In some examples, the heterodimeric protein comprises: (i) the first fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP15902) and the second fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP5908), (ii) the first fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP15902) and the second fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP15909), (iii)

polypeptide sequence of SEQ ID NO:XX (XENP15908), (xxxii) the first fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP17705) and the second fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP15908), (xxxiii) said first fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP18295) and said second fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP17761), (xxxiv) said first fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP18783) and said second fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP15908), (xxxv) said first fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP18784) and said second fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP15908), (xxxvi) said first fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP18786) and said second fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP15908), (xxxvii) said first fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP18788) and said second fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP15908), (xxxviii) said first fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP19242) and said second fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP16481), or (xxxix) said first fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP19243) and said second fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP16481).

[0008] In some instances, the heterodimeric protein is selected from the group consisting of XENP20818, XENP20819, XENP21471, XENP21472, XENP21473, XENP21474, XENP21475, XENP21476, XENP21477, XENP22013, XENP22815, XENP22816, XENP22817, XENP22818, XENP22819, XENP22820, XENP22821, XENP22822, XENP22823, XENP22824, XENP22825, XENP22826, XENP22827, XENP22828, XENP22829, XENP22830, XENP22831, XENP22832, XENP22833, XENP22834, XENP23343, XENP23554, XENP23555, XENP23557, XENP23559, XENP24019, and XENP24020.

[0009] In a further ~~aspect~~example, the present disclosure refers to a heterodimeric protein comprising: a) a fusion protein comprising a first protein domain, a second protein domain, and a first Fc domain, wherein the first protein domain is covalently attached to the N-terminus of the second protein domain using a first domain linker, and wherein the second protein domain is covalently attached to the N-terminus of the first Fc domain using a second domain linker;

b) a second Fc domain; wherein the first and the second Fc domains have a set of amino acid substitutions selected from the group consisting of S267K/L368D/K370S : S267K/S364K/E357Q; S364K/E357Q : L368D/K370S; L368D/K370S : S364K; L368E/K370S : S364K; T411E/K360E/Q362E : D401K; L368D/K370S : S364K/E357L and K370S : S364K/E357Q, according to EU numbering and wherein the first protein domain comprises an IL15Rα protein and the second protein domain comprises an IL15 protein, wherein said IL-15 protein comprises one or more amino acid substitutions selected from the group consisting of N1D, N4D, D8N, D30N, D61N, E64Q, N65D, and Q108E.

[0010] In some examples, the first fusion protein has a polypeptide sequence of SEQ ID NO:XX (16478) and the Fc domain has a polypeptide sequence of SEQ ID NO:XX (8924). The heterodimeric protein can be XENP21478.

[0011] In another ~~aspect~~example, the present disclosure refers to a heterodimeric protein comprising: a) a fusion protein comprising a first protein domain and a first Fc domain, wherein the first protein domain is covalently attached to the N-terminus of the first Fc domain using a domain linker; b) a second Fc domain; and c) a second protein domain noncovalently attached to the first protein domain; wherein the first and the second Fc domains have a set of amino acid substitutions selected from the group consisting of S267K/L368D/K370S : S267K/S364K/E357Q; S364K/E357Q : L368D/K370S; L368D/K370S : S364K; L368E/K370S : S364K; T411E/K360E/Q362E : D401K; L368D/K370S : S364K/E357L and K370S : S364K/E357Q, according to EU numbering and wherein the first protein domain comprises an IL15Rα and the second protein domain comprises an IL15 protein, wherein said IL-15 protein comprises one or more amino acid substitutions selected from the group consisting of N1D, N4D, D8N, D30N, D61N, E64Q, N65D, and Q108E.

[0012] In some examples, the heterodimer protein comprises: (i) the fusion protein having a polypeptide sequence of SEQ ID NO:XX (XENP16481), the second Fc domain having a polypeptide sequence of SEQ ID NO:XX (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:XX (16484); (ii) the fusion protein having a polypeptide sequence of SEQ ID NO:XX (17034), the second Fc domain having a polypeptide sequence of SEQ ID NO:XX (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:XX (16484); (iii) the fusion protein having a polypeptide sequence of SEQ ID NO:XX (17038), the second Fc domain having a polypeptide sequence of SEQ ID NO:XX (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:XX (16484); (iv) the fusion protein having a polypeptide sequence of SEQ ID NO:XX (17036), the second Fc domain having a

[0015] In an additional ~~aspect~~example, the present disclosure refers to a heterodimeric protein comprising: a) a first fusion protein comprising a first Fc domain and a first protein domain, wherein the first Fc domain is covalently attached to the N-terminus of the first protein domain using a domain linker; b) a second Fc domain, and c) a second protein domain noncovalently attached to the first protein domain of the first fusion protein; wherein the first and the second Fc domains have a set of amino acid substitutions selected from the group consisting of S267K/L368D/K370S : S267K/S364K/E357Q; S364K/E357Q : L368D/K370S; L368D/K370S : S364K; L368E/K370S : S364K; T411E/K360E/Q362E : D401K; L368D/K370S : S364K/E357L and K370S : S364K/E357Q, according to EU numbering and wherein the first protein domain comprises an IL15Rα protein and the second protein domain comprises an IL15 protein, wherein said IL-15 protein comprises one or more amino acid substitutions selected from the group consisting of N1D, N4D, D8N, D30N, D61N, E64Q, N65D, and Q108E.

[0016] In some examples, the heterodimer protein comprises (i) the first fusion protein having a polypeptide sequence of SEQ ID NO: XX (17603), the second Fc domain having a polypeptide sequence of SEQ ID NO: XX (8927), and the second protein domain having a polypeptide sequence of SEQ ID NO: XX (16484); or ii) the first fusion protein having a polypeptide sequence of SEQ ID NO: XX (17605), the second Fc domain having a polypeptide sequence of SEQ ID NO: XX (8927), and the second protein domain having a polypeptide sequence of SEQ ID NO: XX (17074).

[0017] In any of the examples of the present disclosure, the first and/or the second Fc domains can have an additional set of amino acid substitutions comprising Q295E/N384D/Q418E/N421D, according to EU numbering. In some cases, the first and/or the second Fc domains have an additional set of amino acid substitutions consisting of G236R/L328R, E233P/L234V/L235A/G236del/S239K, E233P/L234V/L235A/G236del/S267K, E233P/L234V/L235A/G236del/S239K/A327G, E233P/L234V/L235A/G236del/S267K/A327G and E233P/L234V/L235A/G236del, according to EU numbering.

[0018] In any of the examples of the present disclosure, the IL15 protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:1 (full-length human IL15) and SEQ ID NO:2 (truncated human IL15), and the IL15Rα protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:3 (full-length human IL15Rα) and SEQ ID NO:4 (sushi domain of human IL15Rα). In some cases, the IL15

XENP21474, XENP21475, XENP21476, XENP21477, XENP22013, XENP22815, XENP22816, XENP22817, XENP22818, XENP22819, XENP22820, XENP22821, XENP22822, XENP22823, XENP22824, XENP22825, XENP22826, XENP22827, XENP22828, XENP22829, XENP22830, XENP22831, XENP22832, XENP22833, XENP22834, XENP23343, XENP23504, XENP23554, XENP23555, XENP23557, XENP23559, XENP24019, XENP24020, XENP24045, XENP24051, XENP24052, XENP24113, XENP24301, XENP24306, XENP24341, XENP21478, XENP21479, XENP22357, XENP22354, XENP22355, XENP22356, XENP22357, XENP22358, XENP22359, XENP22360, XENP22361, XENP22362, XENP22363, XENP22364, XENP22365, XENP22366, XENP22637, XENP24349, XENP24383, XENP21978, XENP22634, XENP24342, XENP24306, XENP22637, and XENP22639. In an additional example, there is provided an expression vector composition comprising one or more expression vectors each comprising a nucleic acid such that the one or more expression vectors encode a heterodimeric protein selected from the group consisting of XENP20818, XENP20819, XENP21471, XENP21472, XENP21473, XENP21474, XENP21475, XENP21476, XENP21477, XENP22013, XENP22815, XENP22816, XENP22817, XENP22818, XENP22819, XENP22820, XENP22821, XENP22822, XENP22823, XENP22824, XENP22825, XENP22826, XENP22827, XENP22828, XENP22829, XENP22830, XENP22831, XENP22832, XENP22833, XENP22834, XENP23343, XENP23504, XENP23554, XENP23555, XENP23557, XENP23559, XENP24019, XENP24020, XENP24045, XENP24051, XENP24052, XENP24113, XENP24301, XENP24306, XENP24341, XENP21478, XENP21479, XENP22357, XENP22354, XENP22355, XENP22356, XENP22357, XENP22358, XENP22359, XENP22360, XENP22361, XENP22362, XENP22363, XENP22364, XENP22365, XENP22366, XENP22637, XENP24349, XENP24383, XENP21978, XENP22634, XENP24342, XENP24306, XENP22637, and XENP22639. Nucleic acids, expression vectors and host cells are all provided as well, in addition to methods of making these proteins and treating patients with them.

[0019a] In an additional ~~aspect~~example, the present disclosure refers to a nucleic acid composition encoding the first fusion protein disclosed herein. In an additional example ~~aspect~~, the present disclosure refers to a nucleic acid composition encoding the second fusion protein disclosed herein. In an additional example~~aspect~~, the present disclosure refers to an expression vector comprising the nucleic acid composition disclosed herein. In an additional ~~aspect~~example, the present disclosure refers to a host cell comprising one or

more expression vectors disclosed herein. In an additional ~~aspect~~example, the present disclosure refers to a nucleic acid composition encoding the fusion protein disclosed herein. In an additional ~~aspect~~example, the present disclosure refers to a nucleic acid composition encoding the second Fc domain disclosed herein. In an additional ~~aspect~~example, the present disclosure refers to a host cell comprising one or two expression vectors disclosed herein. In another ~~aspect~~example, the present disclosure refers to a host cell comprising the nuclide acid composition disclosed herein. In another example, there is provided a host cell comprising the expression vector composition disclosed herein. In an additional example, there is provided a method of producing the heterodimeric protein disclosed herein comprising culturing the host cell disclosed herein under suitable conditions wherein said heterodimeric protein is expressed, and recovering said protein. In an additional example, there is provided use of a therapeutically effective amount of the heterodimeric protein disclosed herein in the manufacture of a medicament for treating cancer in a patient in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] Figure 1 depicts the structure of IL-15 in complex with its receptors IL-15Rα (CD215), IL-15Rβ (CD122), and the common gamma chain (CD132).

[0021] Figures 2A-2B depict the sequences for IL-15 and its receptors. Figure 2A shows the sequences for human IL-15, human IL-15Rα and human IL-15Rβ. Figure 2A shows the sequences for the human common gamma receptor.

[0022] Figures 3A-3E depict useful pairs of Fc heterodimerization variant sets (including skew and pI variants). On Figures 3D and 3E, there are variants for which there are no corresponding "monomer 2" variants; these are pI variants which can be used alone on either monomer.

WHAT IS CLAIMED IS:

1. A heterodimeric protein comprising:

a) a first fusion protein comprising ~~a first protein domain and a first Fc domain, wherein said first protein domain is~~ an interleukin-15 (IL-15) protein covalently attached to the N-terminus of ~~said~~ a first Fc domain ~~using~~ via a first domain linker, wherein the IL-15 protein comprises the amino acid sequence NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIH DTVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS and wherein the first Fc domain comprises the amino acid sequence EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFN WYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK; and

b) a second fusion protein comprising ~~a second protein domain and a second Fc domain, wherein said second protein domain is~~ an IL-15 receptor alpha (IL-15Rα) protein covalently attached to the N-terminus of ~~said~~ a second Fc domain ~~using~~ via a second domain linker, wherein the IL-15Rα protein comprises the amino acid sequence ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPS LKCIR and wherein the second Fc domain comprises the amino acid sequence EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK~~;~~

~~wherein said first and said second Fc domains have a set of amino acid substitutions selected from the group consisting of S267K/L368D/K370S : S267K/S364K/E357Q; S364K/E357Q : L368D/K370S; L368D/K370S : S364K; L368E/K370S : S364K; T411E/K360E/Q362E : D401K; L368D/K370S : S364K/E357L and K370S : S364K/E357Q, according to EU numbering and wherein said first protein domain comprises an IL15 protein and said second protein domain comprises an IL15Rα protein,~~

~~wherein said IL-15 protein comprises one or more amino acid substitutions selected from the group consisting of N1D, N4D, D8N, D30N, D61N, E64Q, N65D, and Q108E~~.

~~2. The heterodimeric protein according to claim 1, wherein said first and/or said second Fc domains have an additional set of amino acid substitutions comprising Q295E/N384D/Q418E/N421D, according to EU numbering.~~

~~3. The heterodimeric protein according to claim 1 or 2, wherein said first and/or said second Fc domains have an additional set of amino acid substitutions consisting of G236R/L328R, E233P/L234V/L235A/G236del/S239K, E233P/L234V/L235A/G236del/S267K, E233P/L234V/L235A/G236del/S239K/A327G, E233P/L234V/L235A/G236del/S267K/A327G and E233P/L234V/L235A/G236del, according to EU numbering.~~

~~4. The heterodimeric protein according to any one of claims 1 to 3, wherein said IL15 protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:1 (full length human IL15) and SEQ ID NO:2 (truncated human IL15), and said IL15Rα protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:3 (full-length human IL15Rα) and SEQ ID NO:4 (sushi domain of human IL15Rα).~~

~~5. The heterodimeric protein according to any one of claims 1 to 4, wherein said IL15 protein has one or more amino acid substitutions selected from the group consisting of N1D, N4D, D8N, D30N, D61N, E64Q, N65D, and Q108E.~~

~~6. The heterodimeric protein according to any one of claims 1 to 5, wherein said IL15 protein and said IL15Rα protein have a set of amino acid substitutions or additions selected from the group consisting of E87C : D96/P97/C98; E87C : D96/C97/A98; V49C : S40C; L52C : S40C; E89C : K34C; Q48C : G38C; E53C : L42C; C42S : A37C; and L45C : A37C, respectively.~~

2. The heterodimeric protein according to claim 1, wherein the first domain linker comprises the amino acid sequence GGGGS.

3. The heterodimeric protein according to claim 1, wherein the second domain linker comprises the amino acid sequence GGGGS.

4. The heterodimeric protein according to claim 1, wherein the first domain linker comprises the amino acid sequence GGGGS and the second domain linker comprises the amino acid sequence GGGGS.

5. The heterodimeric protein according to any one of claims 1 to 4, wherein the first fusion protein comprises the amino acid sequence NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHD TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSEPKSS DKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDG VEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK.

6. The heterodimeric protein according to any one of claims 1 to 4, wherein the second fusion protein comprises the amino acid sequence ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSL KCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK.

7. ~~The~~ A heterodimeric protein comprising a first fusion protein and a second fusion protein, wherein the first fusion protein comprises the amino acid sequence NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHD TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSEPKSS DKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDG VEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK and the second fusion protein comprises the amino acid sequence ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSL KCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK

ALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK~~a~~

~~ccording to any one of claims 1 to 6, wherein said heterodimeric protein comprises:~~

~~i) said first fusion protein having a polypeptide sequence of SEQ ID NO:52 (15902) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~ii) said first fusion protein having a polypeptide sequence of SEQ ID NO:52 (15902) and said second fusion protein having a polypeptide sequence of SEQ ID NO:421 (15909),~~

~~iii) said first fusion protein having a polypeptide sequence of SEQ ID NO:58 (16479) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~iv) said first fusion protein having a polypeptide sequence of SEQ ID NO:52 (15902) and said second fusion protein having a polypeptide sequence of SEQ ID NO:71 (16481),~~

~~v) said first fusion protein having a polypeptide sequence of SEQ ID NO:52 (15902) and said second fusion protein having a polypeptide sequence of SEQ ID NO:439 (16483),~~

~~vi) said first fusion protein having a polypeptide sequence of SEQ ID NO:58 (16479) and said second fusion protein having a polypeptide sequence of SEQ ID NO:421 (15909),~~

~~vii) said first fusion protein having a polypeptide sequence of SEQ ID NO:58 (16479) and said second fusion protein having a polypeptide sequence of SEQ ID NO:71 (16481),~~

~~viii) said first fusion protein having a polypeptide sequence of SEQ ID NO:454 (16480) and said second fusion protein having a polypeptide sequence of SEQ ID NO:457(16482),~~

ix) said first fusion protein having a polypeptide sequence of SEQ ID NO:454 (16480) and said second fusion protein h having as a polypeptide sequence of SEQ ID NO:421 (15909),

x) said first fusion protein having a polypeptide sequence of SEQ ID NO:597 (17074) and said second fusion protein having a polypeptide sequence of SEQ ID NO:599 (17038),

xi) said first fusion protein having a polypeptide sequence of SEQ ID NO:597 (17074) and said second fusion protein having a polypeptide sequence of SEQ ID NO:609 (17040), or

xii) said first fusion protein having a polypeptide sequence of SEQ ID NO:170 (17072) and said second fusion protein having a polypeptide sequence of SEQ ID NO:614 (17044),

xiii) said first fusion protein having a polypeptide sequence of SEQ ID NO:729 (17686) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),

xiv) said first fusion protein having a polypeptide sequence of SEQ ID NO:735 (17687) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),

xv) said first fusion protein having a polypeptide sequence of SEQ ID NO:741 (17688) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),

xvi) said first fusion protein having a polypeptide sequence of SEQ ID NO:747 (17689) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),

xvii) said first fusion protein having a polypeptide sequence of SEQ ID NO:753 (17690) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),

~~xviii) said first fusion protein having a polypeptide sequence of SEQ ID NO:759(17691) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xix) said first fusion protein having a polypeptide sequence of SEQ ID NO:228 (17692) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xx) said first fusion protein having a polypeptide sequence of SEQ ID NO:234 (17693) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxi) said first fusion protein having a polypeptide sequence of SEQ ID NO:777 (17694) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxii) said first fusion protein having a polypeptide sequence of SEQ ID NO:783 (17695) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxiii) said first fusion protein having a polypeptide sequence of SEQ ID NO:789 (17696) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxiv) said first fusion protein having a polypeptide sequence of SEQ ID NO:795 (17697) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxv) said first fusion protein having a polypeptide sequence of SEQ ID NO:801 (17698) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxvi) said first fusion protein having a polypeptide sequence of SEQ ID NO:807 (17699) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxvii) said first fusion protein having a polypeptide sequence of SEQ ID NO:819 (17701) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxviii) said first fusion protein having a polypeptide sequence of SEQ ID NO:759 (17691) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxix) said first fusion protein having a polypeptide sequence of SEQ ID NO:825 (17702) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxx) said first fusion protein having a polypeptide sequence of SEQ ID NO:831 (17703) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxxi) said first fusion protein having a polypeptide sequence of SEQ ID NO:837 (17704) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxxii) said first fusion protein having a polypeptide sequence of SEQ ID NO:843 (17705) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxxiii) said first fusion protein having a polypeptide sequence of SEQ ID NO:859 (18295) and said second fusion protein having a polypeptide sequence of SEQ ID NO:862 (17761),~~

~~xxxiv) said first fusion protein having a polypeptide sequence of SEQ ID NO:240 (18783) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxxv) said first fusion protein having a polypeptide sequence of SEQ ID NO:887 (18784) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxxvi) said first fusion protein having a polypeptide sequence of SEQ ID NO:246 (18786) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxxvii) said first fusion protein having a polypeptide sequence of SEQ ID NO:899 (18788) and said second fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908),~~

~~xxxviii) said first fusion protein having a polypeptide sequence of SEQ ID NO:264 (19242) and said second fusion protein having a polypeptide sequence of SEQ ID NO:71 (16481), or~~

~~xxxix) said first fusion protein having a polypeptide sequence of SEQ ID NO:955 (19243) and said second fusion protein having a polypeptide sequence of SEQ ID NO:71 (16481)~~.

8. A heterodimeric protein comprising:

a) a first fusion protein comprising an interleukin-15 (IL-15) protein covalently attached to the N-terminus of a first Fc domain via a first domain linker, wherein the IL-15 protein comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHD TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS and wherein the first Fc domain comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNW YVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK; and

b) a second fusion protein comprising an IL-15 receptor alpha (IL-15Rα) protein covalently attached to the N-terminus of a second Fc domain via a second domain linker, wherein the IL-15Rα protein comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence

ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSL KCIR and wherein the second Fc domain comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK.

9. The heterodimeric protein according to claim 8, wherein the first domain linker comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence GGGGS.

10. The heterodimeric protein according to claim 8, wherein the second domain linker comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence GGGGS.

11. The heterodimeric protein according to claim 8, wherein the first domain linker comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence GGGGS and the second domain linker comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence GGGGS.

12. The heterodimeric protein according to any one of claims 8 to 11, wherein the first fusion protein comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHD TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSEPKSS DKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDG VEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK.

13. The heterodimeric protein according to any one of claims 8 to 11, wherein the second fusion protein comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence

ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSL
KCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK.

14. A heterodimeric protein comprising a first fusion protein and a second fusion protein, wherein the first fusion protein comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHD
TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSEPKSS
DKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDG
VEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK and the second fusion protein comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSL
KCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK.

~~8. The heterodimeric protein according to any one of claims 1 to 7, wherein said first protein domain is covalently attached to the N-terminus of said first Fc domain directly and without using said first domain linker and/or said second protein domain is covalently attached to the N-terminus of said second Fc domain directly and without using said second domain linker.~~

~~9~~15. A nucleic acid composition comprising:

a) a first nucleic acid encoding the first fusion protein of any one of claims 1 to ~~8~~14; and

b) a second nucleic acid encoding the second fusion protein of any one of claims 1 to 14.

~~10. A nucleic acid composition encoding the second fusion protein of any one of claims 1 to 8.~~

~~11~~16. An expression vector composition comprising:

a) a first expression vector comprising the first nucleic acid ~~composition~~ of claim ~~9~~15; and

b) a second expression vector comprising the second nucleic acid of claim 15.

~~12. An expression vector comprising the nucleic acid composition of claim 10.~~

~~13. The expression vector of claim 12 further comprising the nucleic acid composition of claim 9.~~

~~14~~17. A host cell comprising ~~one or more~~the expression vector~~s~~ composition of ~~any one of~~ claim~~s 11 to 13~~16.

18. A method of producing a heterodimeric protein comprising culturing the host cell of claim 17 under suitable conditions wherein said heterodimeric protein is expressed, and recovering said protein.

19. A composition comprising a human interleukin 15 (IL-15) variant comprising the amino acid sequence NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHD TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS.

20. A nucleic acid encoding the composition comprising the IL-15 variant of claim 19.

21. An expression vector comprising the nucleic acid of claim 20.

22. A host cell comprising the nucleic acid of claim 20 or the expression vector of claim 21.

~~15. A heterodimeric protein comprising:~~

a) a fusion protein comprising a first protein domain, a second protein domain, and a first Fc domain, wherein said first protein domain is covalently attached to the N-terminus of said second protein domain using a first domain linker, and wherein said second protein domain is covalently attached to the N-terminus of said first Fc domain using a second domain linker;

b) a second Fc domain;

wherein said first and said second Fc domains have a set of amino acid substitutions selected from the group consisting of S267K/L368D/K370S : S267K/S364K/E357Q; S364K/E357Q : L368D/K370S; L368D/K370S : S364K; L368E/K370S : S364K; T411E/K360E/Q362E : D401K; L368D/K370S : S364K/E357L and K370S : S364K/E357Q, according to EU numbering and wherein said first protein domain comprises an IL15Rα protein and said second protein domain comprises an IL15 protein, wherein said IL-15 protein comprises one or more amino acid substitutions selected from the group consisting of N1D, N4D, D8N, D30N, D61N, E64Q, N65D, and Q108E.

16. The heterodimeric protein according to claim 15, wherein said first and/or said second Fc domains have an additional set of amino acid substitutions comprising Q295E/N384D/Q418E/N421D, according to EU numbering.

17. The heterodimeric protein according to claim 15 or 16, wherein said first and/or said second Fc domains have an additional set of amino acid substitutions consisting of G236R/L328R, E233P/L234V/L235A/G236del/S239K, E233P/L234V/L235A/G236del/S267K, E233P/L234V/L235A/G236del/S239K/A327G, E233P/L234V/L235A/G236del/S267K/A327G and E233P/L234V/L235A/G236del, according to EU numbering.

18. The heterodimeric protein according to any one of claims 15 to 17, wherein said IL15 protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:1 (full-length human IL15) and SEQ ID NO:2 (truncated human IL15), and said IL15Rα protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:3 (full-length human IL15Rα) and SEQ ID NO:4 (sushi domain of human IL15Rα).

19. The heterodimeric protein according to any one of claims 15 to 18, wherein said IL15 protein and said IL15Rα protein have a set of amino acid substitutions

~~selected from the group consisting of E87C : D96/P97/C98; E87C : D96/C97/A98; V49C : S40C; L52C : S40C; E89C : K34C; Q48C : G38C; E53C : L42C; C42S : A37C; and L45C : A37C, respectively.~~

~~20. The heterodimeric protein according to any one of claims 15 to 19, wherein said first fusion protein has a polypeptide sequence of SEQ ID NO:64 (16478) and said Fc domain has a polypeptide sequence of SEQ ID NO:68 (8924).~~

~~21. A nucleic acid composition encoding the fusion protein of any one of claims 15 to 20.~~

~~22. A nucleic acid composition encoding the second Fc domain of any one of claims 15 to 20.~~

~~23. An expression vector comprising the nucleic acid composition of claim 21.~~

~~24. An expression vector comprising the nucleic acid composition of claim 22.~~

~~25. The expression vector of claim 24, further comprising the nucleic acid composition of claim 21.~~

~~26. A host cell comprising one or two expression vectors of any one of claims 23 to 25.~~

~~27. A heterodimeric protein comprising:~~

~~a) a fusion protein comprising a first protein domain and a first Fc domain, wherein said first protein domain is covalently attached to the N-terminus of said first Fc domain using a domain linker;~~

~~b) a second Fc domain; and~~

~~c) a second protein domain noncovalently attached to said first protein domain;~~

~~wherein said first and said second Fc domains have a set of amino acid substitutions selected from the group consisting of S267K/L368D/K370S :~~

S267K/S364K/E357Q; S364K/E357Q : L368D/K370S; L368D/K370S : S364K; L368E/K370S : S364K; T411E/K360E/Q362E : D401K; L368D/K370S : S364K/E357L and K370S : S364K/E357Q, according to EU numbering and wherein said first protein domain comprises an IL15Rα and said second protein domain comprises an IL15 protein, wherein said IL-15 protein comprises one or more amino acid substitutions selected from the group consisting of N1D, N4D, D8N, D30N, D61N, E64Q, N65D, and Q108E.

28. The heterodimeric protein according to claim 27, wherein said first and/or said second Fc domains have an additional set of amino acid substitutions comprising Q295E/N384D/Q418E/N421D, according to EU numbering.

29. The heterodimeric protein according to claim 27 or 28, wherein said first and/or said second Fc domains have an additional set of amino acid substitutions consisting of G236R/L328R, E233P/L234V/L235A/G236del/S239K, E233P/L234V/L235A/G236del/S267K, E233P/L234V/L235A/G236del/S239K/A327G, E233P/L234V/L235A/G236del/S267K/A327G and E233P/L234V/L235A/G236del, according to EU numbering.

30. The heterodimeric protein according to any one of claims 27 to 29, wherein said IL15 protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:1 (full length human IL15) and SEQ ID NO:2 (truncated human IL15), and said IL15Rα protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:3 (full length human IL15Rα) and SEQ ID NO:4 (sushi domain of human IL15Rα).

31. The heterodimeric protein according to any one of claims 27 to 30, wherein said IL15 protein and said IL15Rα protein have a set of amino acid substitutions selected from the group consisting of E87C : D96/P97/C98; E87C : D96/C97/A98; V49C : S40C; L52C : S40C; E89C : K34C; Q48C : G38C; E53C : L42C; C42S : A37C; and L45C : A37C, respectively.

32. The heterodimeric protein according to any one of claims 27 to 31, wherein said fusion protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:71 (16481), SEQ ID NO:584 (17034), SEQ ID NO:599 (17038), SEQ ID NO:594 (17036), SEQ ID NO:604 (17039), SEQ ID NO:609 (17040), SEQ ID NO:614 (17044), SEQ ID

NO:624 (17041), SEQ ID NO:629 (17043), SEQ ID NO:634 (17045), SEQ ID NO:639 (17042), SEQ ID NO:55 (15908), and SEQ ID NO:92 (17603).

33. The heterodimeric protein according to any one of claims 27 to 32, wherein said second Fc domain has a polypeptide sequence of SEQ ID NO:70 (8793) or SEQ ID NO:95 (8927).

34. The heterodimeric protein according to any one of claims 27 to 33, wherein said second protein domain has a polypeptide sequence selected from the group consisting of SEQ ID NO:69 (16484), SEQ ID NO:123 (17074), SEQ ID NO:543 (17071), SEQ ID NO:129 (17072), SEQ ID NO:622 (17075), SEQ ID NO:627 (17070), SEQ ID NO:632 (17073), and SEQ ID NO:647 (17083).

35. The heterodimeric protein according to any one of claims 27 to 34, wherein said heterodimer protein comprises

i) said fusion protein having a polypeptide sequence of SEQ ID NO:71 (16481), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:69 (16484);

ii) said fusion protein having a polypeptide sequence of SEQ ID NO:584 (17034), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:69 (16484);

iii) said fusion protein having a polypeptide sequence of SEQ ID NO:599 (17038), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:69 (16484);

iv) said fusion protein having a polypeptide sequence of SEQ ID NO:594 (17036), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:69 (16484);

v) said fusion protein having a polypeptide sequence of SEQ ID NO:599 (17038), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:123 (17074);

vi) said fusion protein having a polypeptide sequence of SEQ ID NO:604 (17039), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:123 (17074);

vii) said fusion protein having a polypeptide sequence of SEQ ID NO:609 (17040), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:123 (17074);

viii) said fusion protein having a polypeptide sequence of SEQ ID NO:614 (17044), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:543 (17071);

ix) said fusion protein having a polypeptide sequence of SEQ ID NO:614 (17044), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:129 (17072);

x) said fusion protein having a polypeptide sequence of SEQ ID NO:622 (17075), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:624 (17041);

xi) said fusion protein having a polypeptide sequence of SEQ ID NO:629 (17043), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:627 (17070);

xii) said fusion protein having a polypeptide sequence of SEQ ID NO:634 (17045), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:632 (17073);

xiii) said fusion protein having a polypeptide sequence of SEQ ID NO:639 (17042), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:647 (17083); or

xiv) said fusion protein having a polypeptide sequence of SEQ ID NO:55 (15908), said second Fc domain having a polypeptide sequence of SEQ ID NO:70 (8793), and a second protein domain having a polypeptide sequence of SEQ ID NO:69 (16484).

~~36. A nucleic acid composition encoding the fusion protein of any one of claims 27 to 35.~~

~~37. A nucleic acid composition encoding the second Fc domain of any one of claims 27 to 35.~~

~~38. An expression vector comprising the nucleic acid composition of claim 36.~~

~~39. An expression vector comprising the nucleic acid composition of claim 37.~~

~~40. The expression vector of claim 39, further comprising the nucleic acid composition of claim 36.~~

~~41. The expression vector of any one of claims 38 to 40, further comprising a nucleic acid composition encoding said second protein domain.~~

~~42. A host cell comprising one or more expression vectors of any one of claims 38 to 41.~~

~~43. A heterodimeric protein comprising:~~

~~a) a first fusion protein comprising a first protein domain and a first Fc domain, wherein said first protein domain is covalently attached to the N-terminus of said first Fc domain using a domain linker;~~

~~b) a second fusion protein comprising a second heavy chain comprising a second protein domain and a first second heavy chain comprising a second Fc domain, wherein said second protein domain is covalently attached to the C-terminus of said second Fc domain using a domain linker;~~

~~c) a third protein domain noncovalently attached to said first protein domain of said first fusion protein; and~~

~~d) a fourth protein domain noncovalently attached to said second protein domain of said second fusion protein,~~

~~wherein said first and said second Fc domains have a set of amino acid substitutions selected from the group consisting of S267K/L368D/K370S : S267K/S364K/E357Q; S364K/E357Q : L368D/K370S; L368D/K370S : S364K; L368E/K370S : S364K; T411E/K360E/Q362E : D401K; L368D/K370S : S364K/E357L and K370S : S364K/E357Q, according to EU numbering and wherein said first protein domain and said second protein domain comprise an IL15Rα protein, and wherein said third protein domain and said fourth protein domain comprises an IL15 protein, wherein said IL-15 protein comprises one or more amino acid substitutions selected from the group consisting of N1D, N4D, D8N, D30N, D61N, E64Q, N65D, and Q108E.~~

~~44. The heterodimeric protein according to claim 43, wherein said first and/or said second Fc domains have an additional set of amino acid substitutions comprising Q295E/N384D/Q418E/N421D, according to EU numbering.~~

~~45. The heterodimeric protein according to claim 43 or 44, wherein said first and/or said second Fc domains have an additional set of amino acid substitutions consisting of G236R/L328R, E233P/L234V/L235A/G236del/S239K, E233P/L234V/L235A/G236del/S267K, E233P/L234V/L235A/G236del/S239K/A327G, E233P/L234V/L235A/G236del/S267K/A327G and E233P/L234V/L235A/G236del, according to EU numbering.~~

~~46. The heterodimeric protein according to any one of claims 43 to 45, wherein said IL15 protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:1 (full-length human IL15) and SEQ ID NO:2 (truncated human IL15), and said IL15Rα protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:3 (full-length human IL15Rα) and SEQ ID NO:4 (sushi domain of human IL15Rα).~~

~~47. The heterodimeric protein according to any one of claims 43 to 46, wherein said IL15 protein and said IL15Rα protein have a set of amino acid substitutions selected from the group consisting of E87C : D96/P97/C98; E87C : D96/C97/A98; V49C : S40C; L52C : S40C; E89C : K34C; Q48C : G38C; E53C : L42C; C42S : A37C; and L45C : A37C, respectively.~~

~~48. The heterodimeric protein according to any one of claims 43 to 47, wherein said heterodimer protein comprises:~~

i) said first fusion protein has a polypeptide sequence of SEQ ID NO:480 (17023) said second fusion protein has a polypeptide sequence of SEQ ID NO:480 (17023), said third protein domain has a polypeptide sequence of SEQ ID NO:69 (16484), and said fourth protein domain has a polypeptide sequence of SEQ ID NO:69 (16484) or

ii) said first fusion protein has a polypeptide sequence of SEQ ID NO:179 (17581), said second fusion protein has a polypeptide sequence of SEQ ID NO:179 (17581), said third protein domain has a polypeptide sequence of SEQ ID NO:123 (17074), and said fourth protein domain has a polypeptide sequence of SEQ ID NO:123 (17074).

49. A nucleic acid composition encoding the first fusion protein of any one of claims 43 to 48.

50. A nucleic acid composition encoding the second fusion protein of any one of claims 43 to 48.

51. An expression vector comprising the nucleic acid composition of claim 49.

52. An expression vector comprising the nucleic acid composition of claim 50.

53. The expression vector of claim 52, further comprising the nucleic acid composition of claim 49.

54. The expression vector of any one of claims 51 to 53, further comprising a nucleic acid composition encoding said third protein domain.

55. The expression vector of any one of claims 51 to 54, further comprising a nucleic acid composition encoding said fourth protein domain.

56. A host cell comprising one or more expression vectors of any one of claims 52 to 55.

57. A heterodimeric protein comprising:

a) a first fusion protein comprising a first Fc domain and a first protein domain, wherein said first Fc domain is covalently attached to the N-terminus of said first protein domain using a domain linker;

b) a second Fc domain, and

c) a second protein domain noncovalently attached to said first protein domain of said first fusion protein;

wherein said first and said second Fc domains have a set of amino acid substitutions selected from the group consisting of S267K/L368D/K370S : S267K/S364K/E357Q; S364K/E357Q : L368D/K370S; L368D/K370S : S364K; L368E/K370S : S364K; T411E/K360E/Q362E : D401K; L368D/K370S : S364K/E357L and K370S : S364K/E357Q, according to EU numbering and wherein said first protein domain comprises an IL15Rα protein and said second protein domain comprises an IL15 protein, wherein said IL-15 protein comprises one or more amino acid substitutions selected from the group consisting of N1D, N4D, D8N, D30N, D61N, E64Q, N65D, and Q108E.

58. The heterodimeric protein according to claim 57, wherein said first and/or said second Fc domains have an additional set of amino acid substitutions comprising Q295E/N384D/Q418E/N421D, according to EU numbering.

59. The heterodimeric protein according to claim 57 or 58, wherein said first or said second Fc domains have an additional set of amino acid substitutions consisting of G236R/L328R, E233P/L234V/L235A/G236del/S239K, E233P/L234V/L235A/G236del/S267K, E233P/L234V/L235A/G236del/S239K/A327G, E233P/L234V/L235A/G236del/S267K/A327G and E233P/L234V/L235A/G236del, according to EU numbering.

60. The heterodimeric protein according to any one of claims 57 to 59, wherein said IL15 protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:1 (full-length human IL15) and SEQ ID NO:2 (truncated human IL15), and said IL15Rα protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:3 (full-length human IL15Rα) and SEQ ID NO:4 (sushi domain of human IL15Rα).

61. The heterodimeric protein according to any one of claims 57 to 60, wherein said IL15 protein and said IL15Rα protein have a set of amino acid substitutions selected from the group consisting of E87C : D96/P97/C98; E87C : D96/C97/A98; V49C : S40C; L52C : S40C; E89C : K34C; Q48C : G38C; E53C : L42C; C42S : A37C; and L45C : A37C, respectively.

~~62. The heterodimeric protein according to any one of claims 57 to 61, wherein heterodimeric protein comprises~~

~~i) said first fusion protein having a polypeptide sequence of SEQ ID NO: 92 (17603), said second Fc domain having a polypeptide sequence of SEQ ID NO: 95 (8927), and said second protein domain having a polypeptide sequence of SEQ ID NO: 69 (16484); or~~

~~ii) said first fusion protein having a polypeptide sequence of SEQ ID NO: 191 (17605), said second Fc domain having a polypeptide sequence of SEQ ID NO: 95 (8927), and said second protein domain having a polypeptide sequence of SEQ ID NO: 123 (17074).~~

~~63. A nucleic acid composition encoding the first fusion protein of any one of claims 57 to 62.~~

~~64. A nucleic acid composition encoding the second Fc domain of any one of claims 57 to 62.~~

~~65. An expression vector comprising the nucleic acid composition of claim 63.~~

~~66. An expression vector comprising the nucleic acid composition of claim 64.~~

~~67. The expression vector of claim 66, further comprising the nucleic acid composition of claim 63.~~

~~68. The expression vector of any one of claims 65 to 67, further comprising a nucleic acid composition encoding said second protein domain.~~

~~69. A host cell comprising one or more expression vectors of any one of claims 65 to 68.~~