

the IL-15/IL-15R α complex to NK cells and CD8⁺ T cells expressing IL-2R β 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-15R α -associated complex. It has also been shown that recombinantly produced IL15/IL15R α heterodimer can potently activate T cells. Nevertheless, a short half-life hinders favorable dosing. The present invention solves this problem by providing novel IL15/IL15R α 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

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCCKVTAMKCFLELQVISLESGDASIH
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-15R α) protein covalently attached to the N-terminus of a second Fc domain via a second domain linker, wherein the IL-15R α protein comprises the amino acid sequence

ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTPPS
LKCIR and wherein the second Fc domain comprises the amino acid sequence

EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVLHEALHSHYTQKSLSLSPGK.

[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

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDASIHD
TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSEPKSS
DKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDG
VEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTPPVLDSD
GSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK and the second fusion protein comprises the amino acid sequence

ITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTPSL
KCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQP
ENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK.

[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

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDASIHD
TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS and wherein the first Fc domain comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence

EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNW
YVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTPPV
LDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK; and

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

ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTTPSL
KCIR and wherein the second Fc domain comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFPYSDIAVEWESNGQPENNYKTTTP
VLDSGGSFFLYSKLTVDKSRWQQGNVFCFVLSHSHYTKQKSLSPGK.

[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

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDASIHD
TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTEGGGGSEPKSS
DKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDG
VEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPYSDIAVEWESDGPENNYKTTTPVLDS
GSFFLYSKLTVDKSRWEQGDVFCFVLSHSHYTKQKSLSPGK and the second fusion protein comprises an amino acid sequence encoded by a polynucleotide that encodes the amino acid sequence

ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTTPSL
KCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFPYSDIAVEWESNGQP
ENNYKTTTPVLDSGGSFFLYSKLTVDKSRWQQGNVFCFVLSHSHYTKQKSLSPGK.

[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
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDASIHD
TVQDLIILANNSLSSNGNVTESGCKECEELEEKNKEFLQSFVHIVQMFINTS.

[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 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 second domain 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 IL15 α 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 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 IL15R α 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 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 IL15R α 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 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 IL15 α 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 IL15 α protein has a polypeptide sequence selected from the group consisting of SEQ ID NO:3 (full-length human IL15 α) and SEQ ID NO:4 (sushi domain of human IL15 α). 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 example, the present disclosure refers to a nucleic acid composition encoding the first fusion protein disclosed herein. In an additional example, the present disclosure refers to a nucleic acid composition encoding the second fusion protein disclosed herein. In an additional example, the present disclosure refers to an expression vector comprising the nucleic acid composition disclosed herein. In an additional example, the present disclosure refers to a host cell comprising one or

more expression vectors disclosed herein. In an additional example, the present disclosure refers to a nucleic acid composition encoding the fusion protein disclosed herein. In an additional example, the present disclosure refers to a nucleic acid composition encoding the second Fc domain disclosed herein. In an additional example, the present disclosure refers to a host cell comprising one or two expression vectors disclosed herein. In another example, the present disclosure refers to a host cell comprising the nucleic 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-15R α (CD215), IL-15R β (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-15R α and human IL-15R β . 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 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
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDASIH
DTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTS 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-15R α) protein covalently attached to the N-terminus of a second Fc domain via a second domain linker, wherein the IL-15R α protein comprises the amino acid sequence
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPS
LKCIR and wherein the second Fc domain comprises the amino acid sequence
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVLHEALHSHYTQKSLSLSPGK.

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

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDASIHD
TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSEPKSS
DKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDG
VEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTTPVLDS
GSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK.

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

ITCPPMMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSL
KCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK.

7. A heterodimeric protein comprising a first fusion protein and a second fusion protein, wherein the first fusion protein comprises the amino acid sequence

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDASIHD
TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSEPKSS
DKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDG
VEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTTPVLDS
GSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK and the second fusion protein comprises the amino acid sequence

ITCPPMMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSL
KCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK.

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

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDASIHD
TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS and wherein
the first Fc domain comprises an amino acid sequence encoded by a polynucleotide that
encodes the amino acid sequence
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNW
YVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTTPV
LDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK; and

b) a second fusion protein comprising an IL-15 receptor alpha (IL-15R α) protein covalently attached to the N-terminus of a second Fc domain via a second domain linker, wherein the IL-15R α 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
SKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTTP
VLDSGDSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK.

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

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPCKVTAMKCFLELQVISLESGDASIHD
TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSEPKSS
DKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDG
VEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTTPVLDS
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

ITCPPMMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSL
KCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK.

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

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPCKVTAMKCFLELQVISLESGDASIHD
TVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSEPKSS
DKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDG
VEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTTPVLDS
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
ENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCVSLHEALHSHYTQKSLSLSPGK.

15. A nucleic acid composition comprising:

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

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

16. An expression vector composition comprising:

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

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

17. A host cell comprising the expression vector composition of claim 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
TVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTS.

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.