

WHAT IS CLAIMED IS:

1. A PD-1 targeted IL-15/R α heterodimeric Fc fusion protein comprising:

a) a first monomer comprising, from N- to C-terminal:

i) an IL-15 receptor alpha (IL-15R α) sushi domain;

ii) a first domain linker,

iii) a variant IL-15 domain, and

iv) a second domain linker, and

v) a first variant Fc domain comprising CH2-CH3; and

b) a second monomer comprising, from N- to C-terminal: a heavy chain comprising VH-CH1-hinge-CH2-CH3, wherein said CH2-CH3 is a second variant Fc domain; and

c) a light chain comprising VL-CL;

wherein said VH and VL form an antigen binding domain that binds human PD-1 and have sequences selected from the pairs consisting of 1C11[PD-1]_H3L3 from XENP22553(SEQ ID NOS:186-187), 1C11[PD-1]_H3.234_L3.144 from XENP25806 (SEQ ID NOS:578-579), 1C11[PD-1]_H3.240_L3.148 from XENP25812 (SEQ ID NO:584), 1C11[PD-1]_H3.241_L3.148 from XENP25813 (SEQ ID NO:585), 1C11[PD-1]_H3.241_L3.92 from XENP25819 (SEQ ID NO:591), 1C11[PD-1]_H3.303_L3.152 from XENP26940 (SEQ ID NOS:642 and 1103), 1C11[PD-1]_H3.329_L3.220 from XENP28026 (SEQ ID NOS:708 and 1169), and 1C11[PD-1]_H3.328_L3.152 from XENP28652 (SEQ ID NOS:719 and 1180); and

wherein said first variant and said second variant Fc domains have a set of amino acid substitutions selected from the group consisting of S267K/L368D/K370S : S267K/LS364K/E357Q; S364K/E357Q : L368D/K370S; L368D/K370S : S364K; L368E/K370S : S364K; T411E/K360E/Q362E : D401K; L368D/K370S : S364K/E357L; L368D/K370S : S364K/E357Q; and K370S : S364K/E357Q, respectively and according to EU numbering.

2. The heterodimeric Fc fusion protein according to claim 1, wherein said first variant Fc domain and/or said second variant Fc domain have amino acid substitutions comprising Q295E/N384D/Q418E/N421D, according to EU numbering.

3. The heterodimeric Fc fusion protein according to claim 1 or 2, wherein said first variant and said variant second Fc domains each have amino acid substitutions selected from the group 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 Fc fusion protein according to any one of claims 1 to 3, wherein said first variant and said second variant Fc domains each have amino acid substitution M428L/N434S, according to EU numbering.

5. The heterodimeric Fc fusion protein according to any one of claims 1 to 4, wherein said variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2.

6. The heterodimeric Fc fusion protein according to any one of claims 1 to 5 wherein said variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and amino acid substitutions selected from the group consisting of N4D/N65D, D30N/N65D, and D30N/E64Q/N65D.

7. The heterodimeric Fc fusion protein according to any one of claims 1 to 5, wherein said IL-15 α sushi domain comprises the amino acid sequence of SEQ ID NO:4.

8. The heterodimeric Fc fusion protein according to any one of claims 1 to 7, selected from the group consisting of XENP29482 set forth in SEQ ID NOS 925, 926, and 1216, XENP25937 set forth in SEQ ID NOS: 70-372, and any one depicted in Figure 126A (SEQ ID NOS:925-929), Figure 126B (SEQ ID NOS:930-935), Figure 126C (SEQ ID NOS:936-941), Figure 126D (SEQ ID NOS:942-947), Figure 127A (SEQ ID NOS:948-953), Figure 127B (SEQ ID NOS:954-959), Figure 127C (SEQ ID NOS:960-965), Figure 127D (SEQ ID NOS:966-971), Figure 128A (SEQ ID NOS:972-977), Figure 128B (SEQ ID NOS:978-983), Figure 128C (SEQ ID NOS:984-989), Figure 128D (SEQ ID NOS:990-995), Figure 128E (SEQ ID NOS:996-1001), Figure 128F (SEQ ID NOS:1002-1007), Figure 128G (SEQ ID NOS:1008-1013), Figure 128H (SEQ ID NOS:1014-1019), Figure 128I (SEQ ID NOS:1020-1025), Figure 128J (SEQ ID NOS:1026-1031), Figure 128K (SEQ ID NOS:1032-1035), Figure 128L (SEQ ID NOS:1036-1041).

9. A nucleic acid composition comprising:

- a) a first nucleic acid encoding the first monomer of the heterodimeric Fc fusion protein according to any one of claims 1 to 8;
- b) a second nucleic acid encoding the second monomer of the heterodimeric Fc fusion protein according to any one of claims 1 to 8; and
- c) a third nucleic acid encoding the light chain of the heterodimeric Fc fusion protein according to any one of claims 1 to 8, respectively.

10. An expression vector composition comprising:

- a) a first expression vector comprising said first nucleic acid of claim 9;
 - b) a second expression vector comprising said second nucleic acid of claim 9;
- and
- c) a third expression vector comprising said third nucleic acid of claim 9.

11. A host cell comprising the nucleic acid composition of claim 9 or the expression vector composition of claim 10.

12. A method of producing a PD-1 targeted IL-15/R α heterodimeric Fc fusion protein according to any one of claims 1 to 8 comprising: culturing the host cell of claim 11 under suitable conditions, wherein said heterodimeric Fc fusion protein is expressed; and recovering said protein.

13. A PD-1 targeted IL-15/R α heterodimeric Fc fusion protein selected from the group consisting of XENP29482 set forth in SEQ ID NOS:925, 926, and 1216, XENP25937 set forth in SEQ ID NOS:370-372, and any one depicted in Figure 126A (SEQ ID NOS:925-929), Figure 126B (SEQ ID NOS:930-935), Figure 126C (SEQ ID NOS:936-941), Figure 126D (SEQ ID NOS:942-947), Figure 127A (SEQ ID NOS:948-953), Figure 127B (SEQ ID NOS:954-959), Figure 127C (SEQ ID NOS:960-965), Figure 127D (SEQ ID NOS:966-971), Figure 128A (SEQ ID NOS:972-977), Figure 128B (SEQ ID NOS:978-983), Figure 128C (SEQ ID NOS:984-989), Figure 128D (SEQ ID NOS:990-995), Figure 128E (SEQ ID NOS:996-1001), Figure 128F (SEQ ID NOS:1002-1007), Figure 128G (SEQ ID NOS:1008-1013), Figure 128H (SEQ ID NOS:1014-1019), Figure 128I (SEQ ID NOS:1020-

1025), Figure 128J (SEQ ID NOS:1026-1031), Figure 128K (SEQ ID NOS:1032-1035), Figure 128L (SEQ ID NOS:1036-1041).

14. Use of a PD-1 targeted IL-15/R α heterodimeric Fc fusion protein according to any one of claims 1 to 8 and 13 in the manufacture of a medicament for treating cancer in a patient in need thereof.

15. The use of claim 14, further comprising a therapeutically effective amount of a checkpoint blockade antibody which is to be administered.

16. The use according to claim 15, wherein said checkpoint blockade antibody is selected from the group consisting of an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-TIM3 antibody, an anti-TIGIT antibody, an anti-LAG3 antibody, and an anti-CTLA-4 antibody.

17. The use according to claim 16, wherein said anti-PD-L1 antibody is atezolizumab, avelumab, or durbalumab.