CLAIMS

1. A polypeptide complex comprising an Interleukin-15 (IL-15) variant domain, an IL-15Rα domain, a first dimerization domain and a second dimerization domain, wherein:

the IL-15 variant domain comprises an IL-15 variant peptide of the amino acid sequence of any of SEQ ID Nos: 51-69; and

the first dimerization domain and the second dimerization domain associates together to form a dimer.

2. The polypeptide complex of claim 1, wherein the IL-15Rα domain comprises or consists of a wild-type IL-15Rα protein, an IL-15Rα variant or any fragment thereof that retains IL-15 binding activity, such as a fragment as set forth in SEQ ID No: 2.

3. The polypeptide complex of any of the preceding claims, further comprising one or more antigen-binding moieties, optionally in VHH, Fab, scFv, VH or VL format,

for example, the antigen-binding moiety specifically binds to a target antigen selected from PD-1, PD-L1, PD-L2, CTLA-4, LAG3, TIM-3, TIM4, 4-1BB, OX-40, OX-40L, GITR, A2aR, TIGIT, CD96, PVRIG, CD226, 5T4, VISTA, VSIG3, VSIG4, ICOS, CD28, CD3, CD4, CD8, CD45, CD44v6, CD27, CD47, SIRPAα, SLAMF7, CD24, Siglec10, Siglec15, Siglec8, VSIR, VSIG4, PSGL-1, C5AR1, BTN1A1, BTN3A1, CD70, RANKL, CSF1R, CSF2RB, TNFRSF1/1a/1b, BDCA2, BTLA, C5aR, NKG2A, NKG2D, NKp30, NKp46, CD16a, CD56, CD166, FCGR3, CD2, Neurophilin-1, CCR8, CCR2, CCR4, CCR5, CCR6, CCR7, CCR8, GCGR, CXCR2, CXCR4, CXCR5, CALCRL, ETAR, GLP1R, CX3CR1, GPR1, GPR17, GPR20, GPR30, GPR34, GPR-65, GPCR78, GPRC5D, GPR84, LGR4, LGR5, VEGF, VEGFR, HER2, HER3, Trop2, pCAD, ERα, EGFR, de2-7 EGFR, EGFRvIII, PSMA, PSCA, PSA, TAG-72, SEZ6, SEZ6L, SEZ6L2, SEMA4D, DLL3, GD2, GPC3, KLB, KLRB1, KLRG1, GPC1, PCSK9, EpCAM, p-Cadherin, Caludin 6, Caludin 18.2, FGFR2b, FGFR3, FGFR4, MUC1, MUC13, MUC16, MUC17, MUCL3, FolRa, TfR, TF, TFR, TFPI, c-Met, NY-ESO-1, GUCY2C, LIV-1, Integrin αvβ6, Integrin α10β1, Intergrin α3, Integrin α5β4, Integrin αvβ3, Integrin αvβ8, ROR1, ROR2, PRLR, PTK7, B7-H3, Nectin-4, NetG1, Ax1, CD147, LRRC15, Napi2b, STEAP1, LY6G6D, LYPD1, MACRO, MerTK, MICA, MICB, MSLN, Mkars, G12D, CDH3, CDH6, CDH17, APLA2, CAIX, CD46, CD47, CLDN6, EphA3, Fucosyl-GM1, ITGA3, Kallikrein, MISRII, Podocalyxin, RON, ROBO1, PAUF, PLA2, Podocalyxin, PRLR, PTK7, TM4SF1, TMEFF2, TREAKR, TREM-1, TREM-2, uPARAP, TYRP1, KAAG1, RU2AS, CD146, CD63, Endoglin, Globo H, IGF-1R, TEM1, TEM8, TAX1BP3, ADAM-9, ENPP3, EphA2, EphA3, FcRH5, NaPi3b, TWEAK, DLK1, SORT1, SSTR2, STEAP1, CD25, CD39, GARP, LRRC33, LAIR1, LAMP3, LAP, LEPR, LILRB1, LILRB2, LILRB4, RAGE, FGL1, TPBG, PDGFRB, TGFBR2, CEACAM1, CEACAM5,

CEACAM6, Carcinoembryonic antigen (CEA), ICAM1, A33, CAMPATH-1 (CDw52), Carboanhydrase IX (MN/CA IX), , CD248, PDPN, ITGB1, ITGAV, CD20, CD19, CD21, CD22, CLL, BCMA, DCLK1, DDR1, DLK1, DPEP3, DKK1, CD5, CD13, CD30, CD33, CD34, CD36, CD37, CD38, CD43, CD52, CD55, CD94, CD99, CD7, CD71, CD73, CD74, CD79a, CD79b, CD229, CD132, CD133, G250 , CSF1R (CD115), HLA-DR, HLA-G, HTRA1, TRA-1-60, IGFR, IL-2 receptor, MCSP (Melanoma-associated cell surface chondroitin sulphate proteoglycan), ART1, ASGR1, B7H3, B7-H4, B7H6, CD124, c-Kit (CD117), CD7, Clex12A, Clever-1, IL-13RA2, IL-11RA, IL-31RA, IL-4RA, IFNAR, ActRIIb, IL-7R, SLAMF7, Fms-like tyrosine kinase 3 (FLT-3, CD135), GFRA1, BTLA, GloboH, CSF2RB, chondroitin sulfate proteoglycan 4 (CSPG4), ITGA4, Clec5a, Clec7a, Clec9a, Clec12a, CLEC14, CD205, CD206, CD200R1, CD228, CD229, CD40, CD40L, FcRn, TLR8, TLR9, TNFR2, LTBR, CD44, CD93, PDGF, PDGFR-alpha (CD140a), PDGFR-beta (CD140b), CD146, CD147, CRTH2, TNF-α, TGF-β, IL1RAcP, TSLP, DR5, ST2, fibroblast activating protein (FAP), CDCP1, Derlin1, Tenascin, frizzled 1-10, the vascular antigens VEGFR2 (KDR/FLK1), VEGFR3 (FLT4, CD309), Endoglin, Tie2 and other TAAs, I/O checkpoints, tumor microenvironment targets, or autoimmune and inflammatory diseases associated targets,

preferably, a first antigen-binding moiety is operably linked to the first dimerization domain, and a second antigen-binding moiety is operably linked to the second dimerization domain.

4. The polypeptide complex of claim 3, wherein the first and second antigen-binding moieties are in VHH format and specifically bind to PD-1, optionally the first and second antigen-binding moieties have same amino acid sequences as set forth in SEQ ID No: 80.

5. The polypeptide complex of any of the preceding claims, wherein the first dimerization domain is one chain of an immunoglobulin Fc region, and the second dimerization domain is the other chain of the immunoglobulin Fc region, wherein the Fc region comprises a human IgG Fc such as a human IgG1 Fc, IgG2 Fc, IgG3 Fc, IgG4 Fc, or a variant thereof,

for example, the Fc variant comprises:

(a) a human IgG4 Fc engineered to comprise one or more of the following: S228P mutation, F234A/L235A mutations, M252Y/S254T/T256E mutations and “knob into hole” structure; or

(b) a human IgG1 Fc engineered to comprise one or more of the following: M252Y/S254T/T256E mutations, G236R/L328R mutations and “knob into hole” structure.

6. The polypeptide complex of any of the preceding claims, comprising a first chain and a second chain, wherein the first chain comprises an amino acid sequence as set forth in SEQ ID No: 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 70, 72, 74 or 76, and the second

chain comprises an amino acid sequence as set forth in SEQ ID No: 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 46, 48, 50, 71, 73, 75 or 77,

preferably, wherein:

(a) the first chain comprises an amino acid sequence as set forth in SEQ ID No: 19, and the second chain comprises an amino acid sequence as set forth in SEQ ID No: 20;

(b) the first chain comprises an amino acid sequence as set forth in SEQ ID No: 70, and the second chain comprises an amino acid sequence as set forth in SEQ ID No: 71;

(c) the first chain comprises an amino acid sequence as set forth in SEQ ID No: 72, and the second chain comprises an amino acid sequence as set forth in SEQ ID No: 73;

(d) the first chain comprises an amino acid sequence as set forth in SEQ ID No: 74, and the second chain comprises an amino acid sequence as set forth in SEQ ID No: 75;

(e) the first chain comprises an amino acid sequence as set forth in SEQ ID No: 21, and the second chain comprises an amino acid sequence as set forth in SEQ ID No: 22;

(f) the first chain comprises an amino acid sequence as set forth in SEQ ID No: 23, and the second chain comprises an amino acid sequence as set forth in SEQ ID No: 24;

(g) the first chain comprises an amino acid sequence as set forth in SEQ ID No: 25, and the second chain comprises an amino acid sequence as set forth in SEQ ID No: 26; or

(h) the first chain comprises an amino acid sequence as set forth in SEQ ID No: 76, and the second chain comprises an amino acid sequence as set forth in SEQ ID No: 77.

7. A fusion protein, comprising the IL-15 variant peptide as defined in any of claims 1-6 operably linked to a non-IL-15 moiety, wherein the non-IL-15 moiety is a moiety that can enhance the half-life of the fusion protein in vivo, such as a moiety selected from PEGs, lipids, Fc region, human serum albumin (HSA) and anti-HSA moiety, or is an IL-15Rα domain, optionally the IL-15Rα domain comprises or consists of a wild-type IL-15Rα protein, an IL-15Rα variant or any fragment thereof that retains IL-15 binding activity, such as a fragment as set forth in SEQ ID No: 2.

8. An IL-15 variant peptide consisting of the amino acid sequence of any of SEQ ID Nos: 51-69, such as SEQ ID No: 51.

9. A nucleic acid molecule, comprising a nucleic acid sequence(s) encoding the first and second chain of the polypeptide complex of any of claims 1-6, the fusion protein of claim 7, or the IL-15 variant peptide of claim 8.

10. A host cell or a vector comprising the nucleic acid molecule of claim 9.

11. A pharmaceutical composition comprising the polypeptide complex of any of claims 1-6, the fusion protein of claim 7 or the nucleic acid molecule of claim 9, as well as a pharmaceutically acceptable carrier.

12. An immunoconjugate comprising the polypeptide complex of any of claims 1-6 or the fusion protein of claim 7 conjugated to a moiety selected from a chemical compound (such as a cytotoxic agent, a cytostatic agent), polypeptide, carbohydrate, lipid, nucleic acid or a combination thereof.

13. A method for producing the polypeptide complex of any of claims 1-6 or the fusion protein of claim 7, comprising the steps of:

- culturing a host cell comprising a vector(s) encoding one or both chains of the polypeptide complex or the fusion protein; and
- isolating the polypeptide complex or the fusion protein from the host cell culture.

14. The polypeptide complex of any of claims 1-6, the fusion protein of claim 7 or the nucleic acid molecule of claim 9 for use in treating or preventing cancer, an infectious disease, an immunodeficiency or lymphopenia in a subject.

15. The polypeptide complex, the fusion protein or the nucleic acid molecule for use according to claim 14, wherein the cancer is selected from breast cancer, lung cancer (such as NSCLC), colon cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, lymphoma (such as non-Hodgkin's lymphoma and diffuse large B-cell lymphoma), leukemia (such as chronic lymphocytic leukemia), and multiple myeloma.

16. The polypeptide complex, the fusion protein or the nucleic acid molecule for use according to claim 14 or 15, which further comprises administering an additional anti-tumor therapy, such as cell therapy (including tumor-infiltrating lymphocyte (TIL) therapy, T cell receptor (TCR) therapy, chimeric antigen receptor (CAR) T cell therapy, and NK cell therapy), targeted therapy, chemotherapy and gene therapy (including using lentivirus, AAV, poxvirus, herpes zoster virus, oncolytic virus, or other RNA/DNA vectors for gene delivery),

alternatively, wherein the nucleic acid molecule is delivered to the subject by the cell therapy or the gene therapy.