

CLAIMS

1. A chimeric protein construct comprising an endoplasmic reticulum-associated
5 degradation (ER-associated degradation, ERAD) mechanism protein binding
domain and a targeting domain.
2. The chimeric protein construct of claim 1, wherein the ERAD mechanism
protein binding domain comprises: a transmembrane domain of a viral
endoplasmic reticulum resident protein or a functional variant thereof, and,
10 an endoplasmic reticulum resident domain or a functional variant thereof.
3. The chimeric protein construct of claim 1, wherein the viral endoplasmic
reticulum resident protein is adenovirus E3-19K.
4. The chimeric protein construct of claim 1, wherein the viral endoplasmic
reticulum resident protein is not adenovirus E3-19K.
- 15 5. The chimeric protein construct of claim 4, wherein the viral endoplasmic
reticulum resident protein is selected from at least one of the group consisting of:
HCMV glycoprotein US2, US11, US3, US10, US6, HSV ICP47, CPXV12, BHV
UL49.5, EBV BNFL2a, HCMV UL16, UL141, UL142, HIV Nef, HIV Vpu,
HHV-7 U21, HHV-8 KK3, HHV-8 KK5, MHV-68 MK3, HTLV-1 p12, Cowpox
20 Virus protein CPXV203.
6. The chimeric protein construct of claim 1, further comprising a protein

degradation pathway member (e.g. E3 ubiquitin ligase, proteasome, lysosome) binding domain, and optionally, the protein degradation pathway member binding domain being linked to the ERAD mechanism protein binding domain.

7. The chimeric protein construct of claim 1, wherein the targeting domain
5 comprises an antibody specifically targeting a target protein or a functional fragment thereof (e.g., Fd, Fv, Fab, Fab', F(ab')₂, Fv(scFv), single chain antibody (scFv), nanobody, diabody, triabody or tetrabody).

8. The chimeric protein construct of claim 7, wherein the target protein is a pathogenic protein, optionally, being a tumor-associated protein, a virus-
10 associated protein, an immune function-related protein (including immunosuppressive and immune stimulatory proteins), an autoantigen protein, or a protein associated with neurodegenerative diseases.

9. The chimeric protein construct of claim 7, wherein the target protein is an immune function-related protein selected from the group consisting of: an
15 antigen-presenting molecule (e.g., a MHC class I molecule, a MHC class II molecule, a MICA/B molecule, etc.), an antigen recognition molecule (e.g., TCR, CD123, NKG2D, etc.), an immune checkpoint molecule (e.g., PD-1, PD-L1, CTLA4, TIM3, TIGIT, LAG3, A2AR, BTLA, IDO1, IDO2, TDO, KIR, NOX2, VISTA, SIGLEC7, PVR, etc.), an immune stimulatory/co-stimulatory molecule
20 (e.g., CD3, CD80/86, CD28, etc.).

10. The chimeric protein construct of claim 2, wherein the targeting domain does

not specifically binding TCR.

11. The chimeric protein construct of claim 10, wherein the targeting domain specifically binds MHC I, MHC II, MICA, MICB, ULBP1, ULBP2, ULBP3, ULBP4, ULBP5 and/or ULBP6; and wherein preferably, MHC I is HLA I; and
5 wherein, preferably, MHC II is HLA II.

12. The chimeric protein construct of claim 4, wherein the targeting domain specifically binds a TCR.

13. The chimeric protein construct of claim 12, wherein the virus endoplasmic reticulum resident protein is selected from at least one of the group consisting of:
10 HCMV glycoprotein US2, US11, US3, US10, US6, HSV ICP47, CPXV12, BHV UL49.5, EBV BNFL2a, HCMV UL16, UL141, UL142, HIV Nef, HIV Vpu, HHV-7 U21, HHV-8 KK3, HHV-8 KK5, MHV-68 MK3, HTLV-1 p12, and Cowpox Virus protein CPXV203.

14. The chimeric protein construct of claim 1, which is linked to at least one co-
15 expression moiety.

15. The chimeric protein construct of claim 14, wherein the at least one co-expression moiety is independently selected from the group consisting of: an intact viral ER resident glycoprotein (e.g., HCMV US2, US3, US11, US10, adenovirus E3-K1 9, HCMV US6, HSV ICP47), a chimeric antigen receptor
20 (CAR), a functional T cell receptor (TCR), a chemokine receptor, or a NK-cell-activating receptor.

16. The chimeric protein construct of claim 15, wherein the chemokine receptor is selected from the group consisting of: CCR4, CCR5, CCR6, CCR7, CCR9, CCR2b, CXCR1, CXCR2, and CXCR4.

17. The chimeric protein construct of claim 16, wherein the NK-cell-activating
5 receptor comprises: (a) an extracellular domain (ED) of the NK-cell-activating receptor or a functional variant thereof, (b) a transmembrane domain (TMD) of the NK-cell-activating receptor or a functional variant thereof, and (c) an intracellular domain (ICD) of the NK-cell-activating receptor or a functional variant thereof; and wherein, optionally, a hinge or linker is included among the
10 extracellular domain of the NK-cell-activating receptor or a functional variant thereof, the transmembrane domain of NK-cell-activating receptor or a functional variant thereof, and/or the intracellular domain of the NK-cell-activating receptor or a functional variant thereof.

18. The chimeric protein construct of claim 17, wherein the NK-cell-activating
15 receptor is selected from the group consisting of NKG2D, NKG2C, NKG2E, NKG2F, NKG2H, CD94, KIR2DL4, KIR2DS1, KIR2DS2, KIR2DS4, KIR3DS1, a natural cytotoxic receptor, TRAIL, DNAM-1, CD16a, 2B4, NTB-A, CRACC, and NKp80.

19. The chimeric protein construct of claim 17, wherein the NK-cell-activating
20 receptor is complexed with a CNK signal transduction module.

20. The chimeric protein construct of claim 14, wherein the at least one co-

expression moiety is linked to the chimeric protein construct by a cleavable linker.

21. A nucleic acid molecule encoding the chimeric protein construct of claim 1.

22. A vector comprising the nucleic acid molecule of claim 21, wherein the nucleic acid molecule is operably linked to at least one polynucleotide regulatory

5 element to express a chimeric protein construct encoded by the nucleic acid molecule.

23. An engineered cell expressing the chimeric protein construct of claim 1, or comprising the nucleic acid molecule of claim 21, or comprising the vector of claim 22.

10 24. The engineered cell of claim 23, wherein the cell is an immune cell selected from the group consisting of: a T cell, a natural killer (NK) cell, a B cell, a macrophage, a monocyte, a dendrites cell, a neutrophil, or a $\gamma\delta$ T cell.

25. A pharmaceutical composition or kit, comprising:

(i) the chimeric protein construct of claim 1, or the nucleic acid molecule of claim

15 21, or the vector of claim 22, or the engineered cell of claim 23, and

(ii) pharmaceutically acceptable medium.