CLAIMS

1. A chimeric polypeptide comprising, from N-terminus to C-terminus:

a) an extracellular ligand-binding domain having a binding affinity for a ligand;

b) a hinge domain capable of promoting oligomer formation of the chimeric polypeptide via intermolecular disulfide bonding;

c) a transmembrane domain comprising one or more ligand-inducible proteolytic cleavage sites; and

d) an intracellular domain comprising a human or humanized transcriptional effector,

wherein binding of the ligand to the extracellular ligand-binding domain results in cleavage at the one or more ligand-inducible proteolytic cleavage sites between the transcriptional effector and the hinge domain,

and wherein the chimeric polypeptide does not comprise a LIN-12-Notch repeat (LNR) and/or a heterodimerization domain (HD) of a Notch receptor.

2. The chimeric polypeptide of claim 1, wherein the transmembrane domain further comprises a stop-transfer-sequence, optionally wherein the stop-transfer-sequence comprises an amino acid sequence having at least 80% sequence identity to any one of SEQ ID NO: 31-51.

3. The chimeric polypeptide of claim 1 or 2, wherein the extracellular ligand-binding domain comprises an antigen-binding moiety capable of binding to a ligand on the surface of a cell, optionally wherein the cell is a pathogen, a human cell, or a human tumor cell.

4. The chimeric polypeptide of claim 3, wherein the antigen-binding moiety is selected from the group consisting of an antibody, a nanobody, a diabody, a triabody, a minibody, an F(ab')2 fragment, an F(ab)v fragment, a single domain antibody (sdAb), and a functional fragment thereof, optionally wherein the antigen-binding moiety comprises a scFv.

5. The chimeric polypeptide of claim 3 or 4, wherein the antigen-binding moiety specifically binds to a tumor-associated antigen, optionally selected from the group consisting of CD19, B7H3 (CD276), BCMA (CD269), ALPPL2, CD123, CD171, CD179a, CD20, CD213A2, CD22, CD24, CD246, CD272, CD30, CD33, CD38, CD44v6, CD46, CD71, CD97, CEA, CLDN6, CLECL1, CS-1, EGFR, EGFRvIII, ELF2M, EpCAM, EphA2, Ephrin B2, FAP, FLT3, GD2, GD3, GM3, GPRC5D, HER2 (ERBB2/neu), IGLL1, IL-11Rα, KIT (CD117), MUC1, NCAM, PAP, PDGFR-β, PRSS21, PSCA, PSMA, ROR1, SIRPα, SSEA-4, TAG72, TEM1/CD248, TEM7R, TSHR, VEGFR2, ALPI, citrullinated vimentin, cMet, and Axl.

6. The chimeric polypeptide of any one of claims 1 to 5, wherein the ligand:

(i) comprises a protein or a carbohydrate;

(ii) is selected from cell surface receptors, adhesion proteins, integrins, mucins, lectins, tumor associated antigens, and tumor-specific antigens; and/or

(iii) is a tumor-associated antigen or a tumor-specific antigen.

7. The chimeric polypeptide of any one of claims 1 to 6, wherein the extracellular ligand-binding domain comprises the ligand-binding portion of a receptor.

8. The chimeric polypeptide of any one of claims 1 to 7, wherein the one or more ligand-inducible proteolytic cleavage sites comprises a γ-secretase cleavage site.

9. The chimeric polypeptide of any one of claims 1 to 8, wherein the transcriptional effector comprises: (i) a DNA-binding domain and (ii) an effector domain through which the transcriptional effector exerts it effect, optionally wherein the DNA-binding domain is N-terminally linked to the effector domain.

10. The chimeric polypeptide of claim 9, wherein the DNA-binding domain:

(a) is derived from a human hepatocyte nuclear factor 1 homeobox A (HNF1α) protein, optionally comprising the amino acid sequence of SEQ ID NO: 52 or a functional variant thereof; or

(b) is derived from a human paired box protein (Pax6) protein, optionally comprising the amino acid sequence of SEQ ID NO: 53 or a functional variant thereof.

11. The chimeric polypeptide of claim 9 or 10, wherein the effector domain is selected from the group consisting of a transcriptional activation domain, a transcriptional repressor domain, and an epigenetic effector domain.

12. The chimeric polypeptide of claim 11, wherein the transcriptional activation domain is derived from human nuclear factor NFκB p65 subunit (p65), optionally wherein the effector domain comprises the amino acid sequence of any one of SEQ ID NOS: 54-55 or a functional variant thereof.

13. The chimeric polypeptide of any one of claims 1 to 12, further comprising an additional proteolytic cleavage site, a signal sequence, a detectable label, a tumor-specific cleavage site, a disease-specific cleavage site, and combinations thereof.

14. The chimeric polypeptide of any one of claims 1 to 13, wherein the hinge domain is derived from a CD8α hinge domain or a functional variant thereof, optionally comprising an amino acid sequence having at least 80% sequence identity to SEQ ID NO: 15.

15. The chimeric polypeptide of any one of claims 1 to 14, wherein the transmembrane domain comprises an amino acid sequence having at least 80% sequence identity to any one of SEQ ID NOS: 21-30.

16. The chimeric polypeptide of any one of claims 1 to 15, wherein the chimeric polypeptide comprises an amino acid sequence of a length shorter than 500, shorter than 600, shorter than 700, shorter than 800, or shorter than 900 amino acid residues.

17. The chimeric polypeptide of any one of claims 1 to 16, wherein the domains recited in (a) through (d) are derived from human polypeptides and optionally are substantially non-immunogenic in a human subject.

18. A recombinant nucleic acid comprising a nucleotide sequence encoding a chimeric polypeptide according to any one of claims 1 to 17.

19. The recombinant nucleic acid of claim 18, further comprising a nucleic acid sequence encoding a protein of interest operably linked to a promoter, wherein expression of the protein of interest is modulated by the transcriptional effector.

20. A recombinant cell comprising:

a) a chimeric polypeptide according to any one of claims 1 to 17; and/or

b) a recombinant nucleic acid according to claim 18 or 19.

21. The recombinant cell of claim 20, wherein the recombinant cell is an immune cell, a neuron, an epithelial cell, and endothelial cell, or a stem cell, optionally wherein the immune cell is a B cell, a monocyte, a natural killer cell, a basophil, an eosinophil, a neutrophil, a dendritic cell, a macrophage, a regulatory T cell, a helper T cell, or a cytotoxic T cell.

22. The recombinant cell of claim 20 or 21, further comprising an expression cassette encoding a protein of interest operably linked to a promoter, wherein expression of the protein of interest is modulated by the transcriptional effector.

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and one or more of the following:

a) a recombinant nucleic acid according to claim 18 or 19; and

b) a recombinant cell according to any one of claims 20 to 22.

24. A system comprising one or more of the following:

a) a chimeric polypeptide according to any one of claims 1 to 17;

b) a recombinant nucleic acid according to claim 18 or 19;

c) a recombinant cell according to any one of claims 20 to 22; and

d) a pharmaceutical composition according to claim 23,

for use in therapy.

25. A method for making the recombinant cell according to any one of claims 20 to 22, comprising:

a) providing a cell capable of protein expression;

b) contacting the provided cell with a recombinant nucleic acid according to claim 18 or 19.

26. Use of one or more of the following:

a) a chimeric polypeptide according to any one of claims 1 to 17;

b) a recombinant nucleic acid according to claim 18 or 19;

c) a recombinant cell according to any one of claims 20 to 22; and

d) a pharmaceutical composition according to claim 23,

in the preparation of a medicament for the treatment of cancer, optionally wherein the cancer is a solid tumor, a soft tissue tumor, or a metastatic lesion.