

WHAT IS CLAIMED IS:

1. A single-chain chimeric polypeptide, wherein the single-chain chimeric polypeptide comprises:

- an extracellular antigen-binding domain;
- a transmembrane domain;
- an intracellular signaling domain; and
- a hormone receptor ligand binding domain;

wherein:

the transmembrane domain and the hormone receptor ligand binding domain directly abut each other or are separated by 1 to 500 amino acids; and

the transmembrane domain and the hormone receptor ligand binding domain are not both present in the same endogenous single-chain polypeptide in a mammal; and

wherein the transmembrane domain comprises at least one contiguous amino acid sequence that traverses a lipid bilayer and has α -helical secondary structure in the lipid bilayer when present in a corresponding endogenous polypeptide when expressed in a mammalian cell; and

wherein the hormone receptor ligand binding domain is a ligand binding domain from an estrogen receptor, a progesterone receptor, or an androgen receptor, and

wherein the hormone receptor ligand binding domain is present in the intracellular domain of the single-chain chimeric polypeptide, or is present between the extracellular antigen-binding domain and the transmembrane domain of the single-chain chimeric polypeptide.

2. The single-chain chimeric polypeptide of claim 1, wherein the intracellular signaling domain comprises a costimulatory domain and an immunoreceptor tyrosine-based activation motif (ITAM), wherein the ITAM of the single-chain chimeric antigen receptor preferably comprises a cytoplasmic signaling sequence from CD3 ζ .

3. The single-chain chimeric polypeptide of claim 2, wherein the extracellular antigen-binding domain is selected from the group consisting of: a scFv, a sc(Fv)₂, a VHH domain, and a VNAR domain, wherein the extracellular antigen-binding domain preferably is a scFv.

4. The single-chain chimeric polypeptide of claim 2 or 3, wherein the extracellular antigen-binding domain binds specifically to a single antigen or binds specifically to two different antigens, wherein preferably the single antigen or at least one of the two different antigens is a tumor antigen, such as a tumor antigen selected from the group consisting of: CD19, WT-1, CD22, L1-CAM, ROR-1, CD30, CD125, AFP, CEA, ETA, MAGE, and MUC16, in particular wherein the tumor antigen is CD19.

5. The single-chain chimeric polypeptide of any one of claims 1-4, wherein the transmembrane domain is a transmembrane domain from: α chain of a T cell receptor, β chain of a T cell receptor, ζ chain of a T cell receptor, CD28, CD3 ϵ , CD3 δ , CD3 γ , CD33, CD37, CD64, CD80, CD45, CD4, CD5, CD8 α , CD9, CD16, CD22, CD86, CD134, CD137, or CD154.

6. The single-chain chimeric polypeptide of any one of claims 1-5, wherein the hormone receptor ligand binding domain is a ligand binding domain from an estrogen receptor.

7. The single-chain chimeric polypeptide of any one of claims 1-6, wherein the extracellular hormone receptor ligand binding domain is a ligand binding domain from a human estrogen receptor, wherein the ligand binding domain of the human estrogen receptor preferably has a wildtype sequence, except that it comprises one or both of a substitution at amino acid position 521 and a substitution at amino acid position 537, each numbered relative to the full-length wildtype sequence of human hormone receptor.

8. The single-chain chimeric polypeptide of any one of claims 1-7, wherein the hormone receptor ligand binding domain and the transmembrane domain are separated by

1 to 250 amino acids, by 1 to 100 amino acids, by 1 to 50 amino acids, or by 1 to 25 amino acids.

9. The single-chain chimeric polypeptide of any one of claims 2-8, wherein the costimulatory domain is a cytoplasmic costimulatory domain from CD27, CD28, 4-1BB, OX40, CD30, CD40L, CD40, PD-1, PD-L1, ICOS, LFA-1, CD2, CD7, CD160, LIGHT, BTLA, TIM3, CD244, CD80, LAG3, NKG2C, and B7-H3, in particular from 4-1BB or CD28.

10. A nucleic acid comprising a nucleotide sequence encoding the single-chain chimeric polypeptide of any one of claims 1-9.

11. A vector comprising the nucleic acid of claim 10.

12. An isolated human cell comprising the nucleic acid of claim 10 or the vector of claim 11.

13. An *in vitro* method of inducing the plasma membrane localization of a single-chain chimeric polypeptide in a human cell, the method comprising:

contacting the human cell expressing the single-chain chimeric polypeptide of any one of claims 1-9 with an amount of a hormone or a hormone analogue sufficient to induce localization of the single-chain chimeric polypeptide to the extracellular side of the plasma membrane of the human cell.

14. Use of an isolated human cell expressing the single-chain chimeric polypeptide of any one of claims 1-9 in the manufacture of a medicament for treating cancer in a human subject having cancer,

wherein the antigen binding domain binds specifically to an antigen expressed by the cancer in the human subject.

15. The isolated human cell of claim 12, the method of claim 13, or the use of claim 14, wherein the human cell is a T cell, such as a T cell selected from the group consisting of: a CD8⁺ T cell, a CD4⁺ T cell, a memory T cell, a Treg cell, and a natural killer T cell.