SUMMARY

[0005] The present disclosure provides conditionally active, heterodimeric polypeptides. The conditionally active, heterodimeric polypeptides are active in the presence of a dimerizing agent that induces dimerization of the polypeptides of the heterodimer. A conditionally active, heterodimeric polypeptide of the present disclosure is useful in a variety of research and treatment methods, which are also provided.

[0006] In one aspect, there is provided a heterodimeric, conditionally active polypeptide comprising: a) a first chimeric polypeptide comprising a first member of a dimerization pair and a first heterologous polypeptide; and b) a second chimeric polypeptide comprising a second member of a dimerization pair and a second heterologous polypeptide, wherein the first member of the dimerization pair comprises a ligand-binding domain (LBD) of a nuclear hormone receptor, and the second member of the dimerization pair comprises a co-regulator of the nuclear hormone receptor, or wherein the first member of the dimerization pair is a co-regulator of a nuclear hormone receptor, and the second member of the dimerization pair comprises an LBD of the nuclear hormone receptor; and wherein the first chimeric polypeptide and the second chimeric polypeptide are dimerized in the presence of a dimerization agent that induces binding of the LBD to the co-regulator. In some cases, a) the first heterologous polypeptide is a T-cell receptor (TCR) alpha chain; and b) the second heterologous polypeptide is a TCR beta chain. In some cases: a) the first heterologous polypeptide is a first polypeptide of a chimeric antigen receptor (CAR) heterodimer; and b) the second heterologous polypeptide is a second polypeptide of a CAR heterodimer. In some cases: a) the first heterologous polypeptide is an N-terminal portion of an RNA-guided endonuclease; and b) the second heterologous polypeptide is a C-terminal portion of the RNA-guided endonuclease, wherein dimerization of the first chimeric polypeptide and the second chimeric polypeptide, mediated by the dimerization agent that induces binding of the LBD to the co-regulator, restores enzymatic function of the RNA-guided endonuclease. In some cases, the RNA-guided endonuclease is a class 2 CRISPR/Cas endonuclease. In some cases, the class 2 CRISPR/Cas endonuclease is a type II CRISPR/Cas protein, a type V CRISPR/Cas protein, or a type VI CRISPR/Cas protein. In some cases: a) the first heterologous polypeptide is an N-terminal portion of an enzyme; and b) the second heterologous polypeptide is a C-terminal portion of the enzyme, wherein dimerization of the first chimeric polypeptide and the second chimeric polypeptide restore enzymatic activity of the enzyme. In some cases, the enzyme is a kinase, a protease, a phosphatase, or a caspase. In some cases, the first polypeptide and the second polypeptide exhibit an activity when brought into proximity upon dimerization mediated by the dimerization agent, but do not exhibit the activity individually. In some cases: a) the first heterologous polypeptide is an N-terminal portion of an antigen receptor; and b) the second heterologous polypeptide is a C-terminal portion of the antigen receptor, wherein dimerization of the first chimeric polypeptide and the second chimeric polypeptide restore signaling activity of the antigen receptor. In some cases: a) the first heterologous polypeptide is an N-terminal portion of a

AMREAPTSLSQLLDNSGAPNV (SEQ ID NO:37); ll) CBP-1: DAASKHKQLSELLRGGSGSSI (SEQ ID NO:38); mm) CBP-2: KRKLIQQQLVLLLHAHKCQRR (SEQ ID NO:39); nn) P300: DAASKHKQLSELLRSGSSPNL (SEQ ID NO:40); oo) CIA: GHPPAIQSLINLLADNRYLTA (SEQ ID NO:41); pp) ARA70–1: TLQQQAQQLYSLLGQFNCLTH (SEQ ID NO:42); qq) ARA70–2: GSRETSEKFKLLFQSYNVNDW (SEQ ID NO:43); rr) TIF1: NANYPRSILTSLLLNSSQSST (SEQ ID NO:44); ss) NSD1: IPIEPDYKFSTLLMMLKDMHD (SEQ ID NO:45); tt) SMAP: ATPPPSPLLSELLKKGSLLPT (SEQ ID NO:46); uu) Tip60: VDGHERAMLKRLLRIDSKCLH (SEQ ID NO:47); vv) ERAP140: HEDLDKVKLIEYYLTKNKEGP (SEQ ID NO:48); ww) Nix1: ESPEFCLGLQTLLSLKCCIDL (SEQ ID NO:49); xx) LCoR: AATTQNPVLSKLLMADQDSPL (SEQ ID NO:50); yy) CoRNR1 (N-CoR): MGQVPRTHRLITLADHICQIITQDFARNQV (SEQ ID NO:51); zz) CoRNR2 (N-CoR): NLGLEDIIRKALMG (SEQ ID NO:52); aaa) CoRNR1 (SMRT): APGVKGHQRVVTLAQHISEVITQDTYRHHPQQLSAPLPAP (SEQ ID NO:53); bbb) CoRNR2 (SMRT): NMGLEAIIRKALMG (SEQ ID NO:54); ccc) RIP140-C: RLTKTNPILYYMLQKGGNSVA (SEQ ID NO:55); ddd) RIP140-1: QDSIVLTYLEGLLMHQAAGGS (SEQ ID NO:56); eee) RIP140-2: KGKQDSTLLASLLQSFSSRLQ (SEQ ID NO:57); fff) RIP140-3: CYGVASSHLKTLLKKSKVKDQ (SEQ ID NO:58); ggg) RIP140-4: KPSVACSQLALLLSSEAHLQQ (SEQ ID NO:59); hhh) RIP140-5: KQAANNSLLLHLLKSQTIPKP (SEQ ID NO:60); iii) RIP140-6: NSHQKVTLLQLLLGHKNEENV (SEQ ID NO:61); jjj) RIP140-7: NLLERRTVLQLLLGNPTKGRV (SEQ ID NO:62); kkk) RIP140-8: FSFSKNGLLSRLLRQNQDSYL (SEQ ID NO:63); lll) RIP140-9: RESKSFNVLKQLLLSENCVRD (SEQ ID NO:64); mmm) PRIC285-1: ELNADDAILRELLDESQKVMV (SEQ ID NO:65); nnn) PRIC285-2: YENLPPAALRKLLRAEPERYR (SEQ ID NO:66); ooo) PRIC285-3: MAFAGDEVLVQLLSGDKAPEG (SEQ ID NO:67); ppp) PRIC285-4: SCCYLCIRLEGLLAPTASPRP (SEQ ID NO:68); and qqq) PRIC285-5: PSNKSVDVLAGLLLRRMELKP (SEQ ID NO:69).

[0007] In one aspect, there is provided a heterodimeric, conditionally active receptor comprising: a) a first chimeric polypeptide comprising: i) a first member of a specific binding pair; ii) a first modulatory domain; iii) a first member of a dimerization pair; and iv) a transmembrane domain interposed between the first member of a specific binding pair and the first modulatory domain; and b) a second chimeric polypeptide comprising: i) a transmembrane domain; ii) a second modulatory domain; iii) a second member of the dimerization pair; and iv) an intracellular signaling domain; or comprising: a) a first chimeric polypeptide comprising: i) a first member of a specific binding pair; ii) a modulatory domain; iii) a first member of a dimerization pair; iv) a transmembrane domain interposed between the first member of a specific binding pair and the modulatory domain; and b) a second chimeric polypeptide comprising: i) a second member of the dimerization pair; and ii) an intracellular signaling domain, wherein the first member of the dimerization pair comprises a ligand-binding domain (LBD) of a nuclear hormone receptor, and the second member of the dimerization pair comprises a co-regulator of the

nuclear hormone receptor, or wherein the first member of the dimerization pair is a co-regulator of a nuclear hormone receptor, and the second member of the dimerization pair comprises an LBD of the nuclear hormone receptor, wherein the first chimeric polypeptide and the second chimeric polypeptide are dimerized in the presence of a dimerization agent that induces binding of the LBD to the co-regulator. In some cases, the first polypeptide comprises a hinge region interposed between the first member of the specific binding pair and the transmembrane domain. In some cases, the first member of the specific binding pair is an antibody or antibody fragment, a ligand, a receptor, or a non-antibody-based recognition scaffold. In some cases, the hinge region is an immunoglobulin IgG hinge region or a hinge derived from CD8. In some cases, the first and second modulatory domains are selected from 4-1BB (CD137), CD28, ICOS, BTLA, OX-40, CD27, CD30, GITR, HVEM, DAP10, DAP12, and CD28. In some cases, the intracellular signaling domain is selected from ZAP70 and CD3-zeta. In some cases, the intracellular signaling domain comprises an immunoreceptor tyrosine-based activation motif (ITAM). In some cases, the LBD of the nuclear hormone binding member of the dimerization pair is an LBD of a nuclear hormone receptor selected from estrogen receptor, an ecdysone receptor, a PPARγ receptor, a glucocorticoid receptor, an androgen receptor, a thyroid hormone receptor, a mineralocorticoid receptor, a progesterone receptor, a vitamin D receptor, a PPARβ receptor, a PPARα receptor, a pregnane X receptor, a liver X receptor, a farnesoid X receptor, a retinoid X receptor, a RAR-related orphan receptor, and a retinoic acid receptor. In some cases, the co-regulator of the nuclear hormone receptor is selected from SRC1, GRIP1, AIB1, PGC1a, PGC1b, PRC, TRAP220, ASC2, CBP, P300, CIA, ARA70, TIF1, NSD1, SMAP, Tip60, ERAP140, Nix1, LCoR, N-CoR, SMRT, RIP140, and PRIC285. In some cases, the co-regulator of the nuclear hormone receptor is a peptide selected from a) SRC1: CPSSHSSLTERHKILHRLLQEGSPS (SEQ ID NO:1); b) SRC1–2: SLTARHKILHRLLQEGSPSDI (SEQ ID NO:2); c) SRC3-1: ESKGHKKLLQLLTCSSDDR (SEQ ID NO:3); d) SRC3: PKKENNALLRYLLDRDDPSDV (SEQ ID NO:4); e) PGC-1: AEEPSLLKKLLLAPANT (SEQ ID NO:5); f) PGC1a: QEAEEPSLLKKLLLAPANTQL (SEQ ID NO:6); g) TRAP220–1: SKVSQNPILTSLLQITGNGGS (SEQ ID NO:7); h) NCoR (2051–2075): GHSFADPASNLGLEDIIRKALMGSF (SEQ ID NO:8); i) NR0B1: PRQGSILYSMLTSAKQT (SEQ ID NO:9); j) NRIP1: AANNSLLLHLLKSQTIP (SEQ ID NO:10); k) TIF2: PKKKENALLRYLLDKDDTKDI (SEQ ID NO:11); l) CoRNR Box: DAFQLRQLILRGLQDD (SEQ ID NO:12); m) αβV: SPGSREWFKDMLS (SEQ ID NO:13); n) TRAP220-2: GNTKNHPMLMNLLKDNPAQDF (SEQ ID NO:14); o) EA2: SSKGVLWRMLAEPVSR (SEQ ID NO:15); p) TA1: SRTLQLDWGTLYWSR (SEQ ID NO:16); q) EAB1: SSNHQSSRLIELLSR (SEQ ID NO:17); r) SRC2: LKEKHKILHRLLQDSSSPV (SEQ ID NO:18); s) SRC1-3: QAQQKSLLQQLLTE (SEQ ID NO:19); t) SRC1–1: KYSQTSHKLVQLLTTTAEQQL (SEQ ID NO:20); u) SRC1–2: SLTARHKILHRLLQEGSPSDI (SEQ ID NO:21); v) SRC1–3: KESKDHQLLRYLLDKDEKDLR (SEQ

ITAM. In some cases, the first member of the specific binding pair is a single-chain Fv. In some cases, the first member of the specific binding pair binds an epitope present on a cell, on a solid surface, or a lipid bilayer. In some cases, the cell is a cancer cell. In some cases, the intracellular signaling domain is an intracellular inhibitory domain. In some cases, the intracellular inhibitory domain is derived from a protein selected from the group consisting of: PD-1, CTLA4, HPK1, SHP1, SHP2, Sts1, and Csk.

[0008] In one aspect, there is provided a heterodimeric, conditionally repressible synthetic immune cell receptor (ICR) comprising: a synthetic stimulatory ICR comprising a first member of a dimerization pair linked to the synthetic stimulatory ICR; and a synthetic ICR repressor comprising a second member of the dimerization pair linked to an intracellular inhibitory domain, wherein the first member of the dimerization pair comprises a ligand-binding domain (LBD) of a nuclear hormone receptor, and the second member of the dimerization pair comprises a co-regulator of the nuclear hormone receptor, or wherein the first member of the dimerization pair is a co-regulator of a nuclear hormone receptor, and the second member of the dimerization pair comprises an LBD of the nuclear hormone receptor, wherein the synthetic stimulatory ICR and the synthetic ICR repressor are dimerized in the presence of a dimerization agent that induces binding of the LBD to the co-regulator. In some cases, the synthetic stimulatory ICR comprises an intracellular co-stimulatory domain. In some cases, the intracellular co-stimulatory domain is selected from the group consisting of: 4-1BB (CD137), CD28, ICOS, OX-40, BTLA, CD27, CD30, GITR, and HVEM. In some cases, the first member of a dimerization pair is linked intracellularly to the synthetic stimulatory ICR and the second member of the dimerization pair is linked intracellularly to the intracellular inhibitory domain. In some cases, the synthetic ICR repressor further comprises a transmembrane domain. In some cases, the second member of the dimerization pair is linked intracellularly to the transmembrane domain. In some cases, the second member of the dimerization pair is extracellular and linked to the intracellular inhibitory domain by way of the transmembrane domain. In some cases, the stimulatory ICR binds a soluble antigen. In some cases, the stimulatory ICR binds a cell surface antigen. In some cases, the intracellular inhibitory domain is an inhibitory domain derived from a protein selected from the group consisting of: PD-1, CTLA4, HPK1, SHP1, SHP2, Sts1 and Csk. In some cases, the synthetic stimulatory ICR comprises an intracellular signaling domain selected from the group consisting of: a CD3-zeta signaling domain, a ZAP70 signaling domain and an immunoreceptor tyrosine-based activation motif (ITAM). In some cases, the LBD of the nuclear hormone binding member of the dimerization pair is an LBD of a nuclear hormone receptor selected from estrogen receptor, an ecdysone receptor, a PPARγ receptor, a glucocorticoid receptor, an androgen receptor, a thyroid hormone receptor, a mineralocorticoid receptor, a progesterone receptor, a vitamin D receptor, a PPARβ receptor, a PPARα receptor, a pregnane X receptor, a liver X receptor, a farnesoid X receptor, a retinoid X receptor, a RAR-related orphan receptor, and a retinoic acid receptor. In some cases, the co-regulator of the nuclear hormone receptor is selected from SRC1, GRIP1, AIB1, PGC1a, PGC1b, PRC,

MGQVPRTHRLITLADHICQIITQDFARNQV (SEQ ID NO:51); zz) CoRNR2 (N-CoR): NLGLEDIIRKALMG (SEQ ID NO:52); aaa) CoRNR1 (SMRT): APGVKGHQRVVTLAQHISEVITQDTYRHHPQQLSAPLPAP (SEQ ID NO:53); bbb) CoRNR2 (SMRT): NMGLEAIIRKALMG (SEQ ID NO:54); ccc) RIP140-C: RLTKTNPILYYMLQKGGNSVA (SEQ ID NO:55); ddd) RIP140-1: QDSIVLTYLEGLLMHQAAGGS (SEQ ID NO:56); eee) RIP140-2: KGKQDSTLLASLLQSFSSRLQ (SEQ ID NO:57); fff) RIP140-3: CYGVASSHLKTLLKKSKVKDQ (SEQ ID NO:58); ggg) RIP140-4: KPSVACSQLALLLSSEAHLQQ (SEQ ID NO:59); hhh) RIP140-5: KQAANNSLLLHLLKSQTIPKP (SEQ ID NO:60); iii) RIP140-6: NSHQKVTLLQLLLGHKNEENV (SEQ ID NO:61); jjj) RIP140-7: NLLERRTVLQLLLGNPTKGRV (SEQ ID NO:62); kkk) RIP140-8: FSFSKNGLLSRLLRQNQDSYL (SEQ ID NO:63); lll) RIP140-9: RESKSFNVLKQLLLSENCVRD (SEQ ID NO:64); mmm) PRIC285-1: ELNADDAILRELLDESQKVMV (SEQ ID NO:65); nnn) PRIC285-2: YENLPPAALRKLLRAEPERYR (SEQ ID NO:66); ooo) PRIC285-3: MAFAGDEVLVQLLSGDKAPEG (SEQ ID NO:67); ppp) PRIC285-4: SCCYLCIRLEGLLAPTASPRP (SEQ ID NO:68); and qqq) PRIC285-5: PSNKSVDVLAGLLLRRMELKP (SEQ ID NO:69). In some cases, the synthetic stimulatory ICR is a synthetic chimeric antigen receptor (CAR) or portion thereof. In some cases, the synthetic stimulatory ICR is a synthetic T cell receptor (TCR) or portion thereof.

[0009] The present disclosure provides a heterodimeric, conditionally repressible synthetic chimeric antigen receptor (CAR) comprising: a) a synthetic stimulatory CAR comprising: i) a extracellular recognition domain; ii) a transmembrane domain linked to the extracellular recognition domain; iii) a first member of a dimerization pair linked to the transmembrane domain; and iv) an intracellular stimulation domain; and b) a synthetic CAR repressor comprising: i) a second member of the dimerization pair; and ii) an intracellular inhibitory domain linked to the second member of the dimerization pair, wherein the first member of the dimerization pair comprises a ligand-binding domain (LBD) of a nuclear hormone receptor, and the second member of the dimerization pair comprises a co-regulator of the nuclear hormone receptor, or wherein the first member of the dimerization pair is a co-regulator of a nuclear hormone receptor, and the second member of the dimerization pair comprises an LBD of the nuclear hormone receptor; and wherein the synthetic stimulatory CAR and the synthetic CAR repressor are dimerized in the presence of a ligand that induces binding of the LBD to the co-regulator. In one aspect, there is provided a heterodimeric, conditionally repressible synthetic chimeric antigen receptor (CAR) comprising: a) a synthetic stimulatory CAR comprising: i) an extracellular recognition domain; ii) a transmembrane domain linked to the extracellular recognition domain; iii) a first member of a dimerization pair linked to the transmembrane domain; and iv) an intracellular stimulation domain; and b) a synthetic CAR repressor comprising: i) a second member of the dimerization pair; and ii) an intracellular inhibitory domain linked to the second member of the dimerization pair, wherein the first member of the dimerization pair comprises a ligand-binding domain (LBD) of a nuclear hormone receptor, and the second member of the dimerization pair comprises a co-regulator of the nuclear hormone receptor, or wherein the first member of the dimerization pair is a co-regulator of a nuclear hormone receptor, and the second member of the dimerization pair comprises an LBD of the nuclear hormone receptor; and wherein the synthetic stimulatory CAR and the synthetic CAR repressor are dimerized in the presence of a dimerization agent that induces binding of the LBD to the co-regulator. In some cases, the synthetic CAR repressor further comprises a transmembrane domain linked to the second member of the dimerization pair, the intracellular inhibitory domain or both. In some cases, the LBD of the nuclear hormone binding member of the dimerization pair is an LBD of a nuclear hormone receptor selected from estrogen receptor, an ecdysone receptor, a PPARγ receptor, a glucocorticoid receptor, an androgen receptor, a thyroid hormone receptor, a mineralocorticoid receptor, a progesterone receptor, a vitamin D receptor, a PPARβ receptor, a PPARα receptor, a pregnane X receptor, a liver X receptor, a farnesoid X receptor, a retinoid X receptor, a RAR-related orphan receptor, and a retinoic acid receptor. In some

ID NO:49); xx) LCoR: AATTQNPVLSKLLMADQDSPL (SEQ ID NO:50); yy) CoRNR1 (N-CoR): MGQVPRTHRLITLADHICQIITQDFARNQV (SEQ ID NO:51); zz) CoRNR2 (N-CoR): NLGLEDIIRKALMG (SEQ ID NO:52); aaa) CoRNR1 (SMRT): APGVKGHQRVVTLAQHISEVITQDTYRHHPQQLSAPLPAP (SEQ ID NO:53); bbb) CoRNR2 (SMRT): NMGLEAIIRKALMG (SEQ ID NO:54); ccc) RIP140-C: RLTKTNPILYYMLQKGGNSVA (SEQ ID NO:55); ddd) RIP140-1: QDSIVLTYLEGLLMHQAAGGS (SEQ ID NO:56); eee) RIP140-2: KGKQDSTLLASLLQSFSSRLQ (SEQ ID NO:57); fff) RIP140-3: CYGVASSHLKTLLKKSKVKDQ (SEQ ID NO:58); ggg) RIP140-4: KPSVACSQLALLLSSEAHLQQ (SEQ ID NO:59); hhh) RIP140-5: KQAANNSLLLHLLKSQTIPKP (SEQ ID NO:60); iii) RIP140-6: NSHQKVTLLQLLLGHKNEENV (SEQ ID NO:61); jjj) RIP140-7: NLLERRTVLQLLLGNPTKGRV (SEQ ID NO:62); kkk) RIP140-8: FSFSKNGLLSRLLRQNQDSYL (SEQ ID NO:63); lll) RIP140-9: RESKSFNVLKQLLLSENCVRD (SEQ ID NO:64); mmm) PRIC285-1: ELNADDAILRELLDESQKVMV (SEQ ID NO:65); nnn) PRIC285-2: YENLPPAALRKLLRAEPERYR (SEQ ID NO:66); ooo) PRIC285-3: MAFAGDEVLVQLLSGDKAPEG (SEQ ID NO:67); ppp) PRIC285-4: SCCYLCIRLEGLLAPTASPRP (SEQ ID NO:68); and qqq) PRIC285-5: PSNKSVDVLAGLLLRRMELKP (SEQ ID NO:69).

[0010] In one aspect, there is provided a heterodimeric, conditionally repressible synthetic T cell receptor (TCR) comprising: a) a synthetic stimulatory TCR comprising: i) a transmembrane domain; ii) a first member of a dimerization pair linked to the transmembrane domain; iii) an engineered TCR polypeptide comprising at least one TCR alpha or beta chain, wherein the at least one TCR alpha or beta chain is linked to the transmembrane domain or the first member of a dimerization pair; and b) a synthetic TCR repressor comprising: i) a second member of the dimerization pair; and ii) an intracellular inhibitory domain linked to the second member of the dimerization pair, wherein the first member of the dimerization pair comprises a ligand-binding domain (LBD) of a nuclear hormone receptor, and the second member of the dimerization pair comprises a co-regulator of the nuclear hormone receptor, or wherein the first member of the dimerization pair is a co-regulator of a nuclear hormone receptor, and the second member of the dimerization pair comprises an LBD of the nuclear hormone receptor; and wherein the synthetic stimulatory TCR and the synthetic TCR repressor are dimerized in the presence of a dimerization agent that induces binding of the LBD to the co-regulator. In some cases, the synthetic TCR repressor further comprises a transmembrane domain linked to the second member of the dimerization pair, the intracellular inhibitory domain or both. In some cases, the engineered TCR polypeptide further comprises a TCR gamma chain. In some cases, the LBD of the nuclear hormone binding member of the dimerization pair is an LBD of a nuclear hormone receptor selected from estrogen receptor, an ecdysone receptor, a PPARγ receptor, a glucocorticoid receptor, an androgen receptor, a thyroid hormone receptor, a mineralocorticoid receptor, a progesterone receptor, a vitamin D receptor, a PPARβ receptor, a PPARα receptor, a pregnane X receptor, a liver X receptor, a farnesoid X receptor, a

HEDLDKVKLIEYYLTKNKEGP (SEQ ID NO:48); ww) Nix1: ESPEFCLGLQTLLSLKCCIDL (SEQ ID NO:49); xx) LCoR: AATTQNPVLSKLLMADQDSPL (SEQ ID NO:50); yy) CoRNR1 (N-CoR): MGQVPRTHRLITLADHICQIITQDFARNQV (SEQ ID NO:51); zz) CoRNR2 (N-CoR): NLGLEDIIRKALMG (SEQ ID NO:52); aaa) CoRNR1 (SMRT): APGVKGHQRVVTLAQHISEVITQDTYRHHPQQLSAPLPAP (SEQ ID NO:53); bbb) CoRNR2 (SMRT): NMGLEAIIRKALMG (SEQ ID NO:54); ccc) RIP140-C: RLTKTNPILYYMLQKGGNSVA (SEQ ID NO:55); ddd) RIP140-1: QDSIVLTYLEGLLMHQAAGGS (SEQ ID NO:56); eee) RIP140-2: KGKQDSTLLASLLQSFSSRLQ (SEQ ID NO:57); fff) RIP140-3: CYGVASSHLKTLLKKSKVKDQ (SEQ ID NO:58); ggg) RIP140-4: KPSVACSQLALLLSSEAHLQQ (SEQ ID NO:59); hhh) RIP140-5: KQAANNSLLLHLLKSQTIPKP (SEQ ID NO:60); iii) RIP140-6: NSHQKVTLLQLLLGHKNEENV (SEQ ID NO:61); jjj) RIP140-7: NLLERRTVLQLLLGNPTKGRV (SEQ ID NO:62); kkk) RIP140-8: FSFSKNGLLSRLLRQNQDSYL (SEQ ID NO:63); lll) RIP140-9: RESKSFNVLKQLLLSENCVRD (SEQ ID NO:64); mmm) PRIC285-1: ELNADDAILRELLDESQKVMV (SEQ ID NO:65); nnn) PRIC285-2: YENLPPAALRKLLRAEPERYR (SEQ ID NO:66); ooo) PRIC285-3: MAFAGDEVLVQLLSGDKAPEG (SEQ ID NO:67); ppp) PRIC285-4: SCCYLCIRLEGLLAPTASPRP (SEQ ID NO:68); and qqq) PRIC285-5: PSNKSVDVLAGLLLRRMELKP (SEQ ID NO:69).

[0011] In one aspect, there is provided a heterodimeric, conditionally active chimeric antigen receptor (CAR) comprising: a) a first polypeptide comprising: i) a first member of a specific binding pair; ii) a first modulatory domain; iii) a first member of a dimerization pair; and iv) a transmembrane domain interposed between the first member of a specific binding pair and the first modulatory domain; and b) a second polypeptide comprising: i) a transmembrane domain; ii) a second modulatory domain; iii) a second member of the dimerization pair; and iv) an intracellular signaling domain; or comprising: a) a first polypeptide comprising: i) a first member of a specific binding pair; ii) a modulatory domain; iii) a first member of a dimerization pair; iv) a transmembrane domain interposed between the first member of a specific binding pair and the modulatory domain; and b) a second polypeptide comprising: i) a second member of the dimerization pair; and ii) an intracellular signaling domain, wherein the first member of the dimerization pair comprises a ligand-binding domain (LBD) of a nuclear hormone receptor, and the second member of the dimerization pair comprises a co-regulator of the nuclear hormone receptor, or wherein the first member of the dimerization pair is a co-regulator of a nuclear hormone receptor, and the second member of the dimerization pair comprises an LBD of the nuclear hormone receptor; and wherein the first polypeptide and the second polypeptide are dimerized in the presence of a dimerizing agent that induces binding of the LBD to the co-regulator.In some cases, the first polypeptide comprises a hinge region interposed between the first member of the specific binding pair and the transmembrane domain. In some cases, the first member of the specific binding pair is an antibody or antibody fragment, a ligand, or a receptor. In some cases, the hinge region is an immunoglobulin IgG hinge region or a hinge

PKKKENALLRYLLDKDDTKDI (SEQ ID NO:27); bb) AIB1–1: LESKGHKKLLQLLTCSSDDRG (SEQ ID NO:28); cc) AIB1–2: LLQEKHRILHKLLQNGNSPAE (SEQ ID NO:29); dd) AIB1–3: KKKENNALLRYLLDRDDPSDA (SEQ ID NO:30); ee) PGC1a: QEAEEPSLLKKLLLAPANTQL (SEQ ID NO:31); ff) PGC1b: PEVDELSLLQKLLLATSYPTS (SEQ ID NO:32); gg) PRC: VSPREGSSLHKLLTLSRTPPE (SEQ ID NO:33); hh) TRAP220–1: SKVSQNPILTSLLQITGNGGS (SEQ ID NO:34); ii) TRAP220–2: GNTKNHPMLMNLLKDNPAQDF (SEQ ID NO:35); jj) ASC2–1: DVTLTSPLLVNLLQSDISAGH (SEQ ID NO:36); kk) ASC2–2: AMREAPTSLSQLLDNSGAPNV (SEQ ID NO:37); ll) CBP-1: DAASKHKQLSELLRGGSGSSI (SEQ ID NO:38); mm) CBP-2: KRKLIQQQLVLLLHAHKCQRR (SEQ ID NO:39); nn) P300: DAASKHKQLSELLRSGSSPNL (SEQ ID NO:40); oo) CIA: GHPPAIQSLINLLADNRYLTA (SEQ ID NO:41); pp) ARA70–1: TLQQQAQQLYSLLGQFNCLTH (SEQ ID NO:42); qq) ARA70–2: GSRETSEKFKLLFQSYNVNDW (SEQ ID NO:43); rr) TIF1: NANYPRSILTSLLLNSSQSST (SEQ ID NO:44); ss) NSD1: IPIEPDYKFSTLLMMLKDMHD (SEQ ID NO:45); tt) SMAP: ATPPPSPLLSELLKKGSLLPT (SEQ ID NO:46); uu) Tip60: VDGHERAMLKRLLRIDSKCLH (SEQ ID NO:47); vv) ERAP140: HEDLDKVKLIEYYLTKNKEGP (SEQ ID NO:48); ww) Nix1: ESPEFCLGLQTLLSLKCCIDL (SEQ ID NO:49); xx) LCoR: AATTQNPVLSKLLMADQDSPL (SEQ ID NO:50); yy) CoRNR1 (N-CoR): MGQVPRTHRLITLADHICQIITQDFARNQV (SEQ ID NO:51); zz) CoRNR2 (N-CoR): NLGLEDIIRKALMG (SEQ ID NO:52); aaa) CoRNR1 (SMRT): APGVKGHQRVVTLAQHISEVITQDTYRHHPQQLSAPLPAP (SEQ ID NO:53); bbb) CoRNR2 (SMRT): NMGLEAIIRKALMG (SEQ ID NO:54); ccc) RIP140-C: RLTKTNPILYYMLQKGGNSVA (SEQ ID NO:55); ddd) RIP140-1: QDSIVLTYLEGLLMHQAAGGS (SEQ ID NO:56); eee) RIP140-2: KGKQDSTLLASLLQSFSSRLQ (SEQ ID NO:57); fff) RIP140-3: CYGVASSHLKTLLKKSKVKDQ (SEQ ID NO:58); ggg) RIP140-4: KPSVACSQLALLLSSEAHLQQ (SEQ ID NO:59); hhh) RIP140-5: KQAANNSLLLHLLKSQTIPKP (SEQ ID NO:60); iii) RIP140-6: NSHQKVTLLQLLLGHKNEENV (SEQ ID NO:61); jjj) RIP140-7: NLLERRTVLQLLLGNPTKGRV (SEQ ID NO:62); kkk) RIP140-8: FSFSKNGLLSRLLRQNQDSYL (SEQ ID NO:63); lll) RIP140-9: RESKSFNVLKQLLLSENCVRD (SEQ ID NO:64); mmm) PRIC285-1: ELNADDAILRELLDESQKVMV (SEQ ID NO:65); nnn) PRIC285-2: YENLPPAALRKLLRAEPERYR (SEQ ID NO:66); ooo) PRIC285-3: MAFAGDEVLVQLLSGDKAPEG (SEQ ID NO:67); ppp) PRIC285-4: SCCYLCIRLEGLLAPTASPRP (SEQ ID NO:68); and qqq) PRIC285-5: PSNKSVDVLAGLLLRRMELKP (SEQ ID NO:69). In some cases, the first member of the specific binding pair is a single-chain Fv. In some cases, the first member of the specific binding pair binds an epitope present on a cell, on a solid surface, or a lipid bilayer. In some cases, the cell is a cancer cell.

[0012] In one aspect, here is provided a mammalian cell genetically modified to produce the heterodimeric, conditionally active polypeptide or receptor as described above or elsewhere herein. In some cases, the

cell is a stem cell, a progenitor cell, or a cell derived from a stem cell or a progenitor cell. In some cases, the cell is a T lymphocyte or an NK cell.

[0013] In one aspect, there is provided a nucleic acid comprising nucleotide sequences encoding the heterodimeric, conditionally active receptor or polypeptide as described above or elsewhere herein. In some cases, the nucleotide sequences are operably linked to a promoter. In some cases, the promoter is an inducible promoter. In some cases, the promoter is a cell type-specific or tissue-specific promoter. In some cases, the promoter is a T lymphocyte-specific promoter or an NK cell-specific promoter. In some cases, the nucleic acid is *in vitro* transcribed RNA. The present disclosure provides a recombinant expression vector comprising the nucleic acid. In some cases, the recombinant expression vector is a viral vector, e.g., a lentiviral vector, a retroviral vector, or an adeno-associated viral vector.

[0014] In one aspect, there is provided a method of modulating an activity of a eukaryotic cell, the method comprising: a) expressing the heterodimeric, conditionally active polypeptide or receptor as described above, or elsewhere herein, in the eukaryotic cell; and b) contacting the cell with the ligand.

[0015] The present disclosure provides a method of modulating an activity of a T lymphocyte, the method comprising contacting the T lymphocyte with a dimerizing agent and a second member of a specific binding pair, wherein the T lymphocyte is genetically modified to produce a heterodimeric, conditionally active receptor as described above, or elsewhere herein, and wherein, in the presence of the dimerizing agent and the second member of a specific binding pair, the heterodimeric, conditionally active receptor dimerizes and modulates an activity of the T lymphocyte, thereby producing a modulated T lymphocyte. In some cases, the second member of a specific binding pair is an antigen. In some cases, the contacting occurs *in vivo*. In some cases, the T lymphocyte is activated, thereby producing an activated T lymphocyte. In some cases, the activated T lymphocyte mediates killing of a target cell. In some cases, the activated T lymphocyte produces IL-2 and/or IFN-γ. In some cases, the target cell is a cancer cell.

[0016] In one aspect, there is provided a method of making the cell as described above, or elsewhere herein, the method comprising genetically modifying a mammalian cell with an expression vector comprising nucleotide sequences encoding the heterodimeric, conditionally active receptor or polypeptide as described above or elsewhere herein, or genetically modifying a mammalian cell with an RNA comprising nucleotide sequences encoding the heterodimeric, conditionally active receptor as described above or elsewhere herein. In some cases, the genetic modification is carried out *ex vivo*. In some cases, the cell is a T lymphocyte, a stem cell, an NK cell, a progenitor cell, a cell derived from a stem cell, or a cell derived from a progenitor cell.

[0017] The present disclosure provides a method of treating a cancer in an individual, the method comprising: i) genetically modifying T lymphocytes obtained from the individual with an expression vector comprising nucleotide sequences encoding the heterodimeric, conditionally active chimeric

antigen receptor (CAR) as described above or elsewhere herein, wherein the antigen-binding domain of the heterodimeric, conditionally active CAR is specific for an epitope on a cancer cell in the individual, and wherein said genetic modification is carried out *ex vivo*; ii) introducing the genetically modified T lymphocytes into the individual; and iii) administering to the individual an effective amount of a dimerizing agent, wherein the dimerizing agent induces dimerization of the heterodimeric, conditionally active receptor, wherein said dimerization provides for activation of the genetically modified T lymphocytes and killing of the cancer cell, thereby treating the cancer. In one aspect, there is provided use of an expression vector comprising nucleotide sequences encoding the heterodimeric, conditionally active chimeric antigen receptor (CAR) as described above or elsewhere herein in the manufacture of a medicament for treating a cancer in an individual, wherein: i) T lymphocytes obtained from the individual are to be genetically modified with the medicament, wherein the antigen-binding domain of the heterodimeric, conditionally active CAR is specific for an epitope on a cancer cell in the individual, and wherein said genetic modification is to be carried out ex vivo; ii) the genetically modified T lymphocytes are to be introduced into the individual; and iii) an effective amount of a dimerizing agent is to be administered to the individual, wherein the dimerizing agent induces dimerization of the heterodimeric, conditionally active receptor, wherein said dimerization provides for activation of the genetically modified T lymphocytes and killing of the cancer cell, thereby treating the cancer. In some cases, the dimerizing agent is a nuclear hormone that binds the LBD of the nuclear hormone receptor and the co-regulator.

[0018] The present disclosure provides a method of modulating the activity of a host cell, the method comprising contacting the host cell with a dimerizing agent and a second member of a specific binding pair, wherein the T lymphocyte is genetically modified to produce a heterodimeric, conditionally active receptor as described above or elsewhere herein, and wherein, in the presence of the dimerizing agent and the second member of a specific binding pair, the heterodimeric, conditionally active receptor dimerizes and modulates at least one activity of the host cell. In some cases, the activity is proliferation, cell survival, apoptosis, gene expression, or immune activation. In some cases, the second member of a specific binding pair is an antigen.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A-1F depict amino acid sequences of mineralocorticoid receptors (MR). FIG. 1A: full-length MR amino acid sequence; FIG. 1B-1E: amino acid sequences of ligand-binding domain (LBD) of MR; FIG. 1F: multiple sequence alignment of LBD of MR of various species. (SEQ ID NOs:70-84).

FIG. 2A-2I depict amino acid sequences of androgen receptors (AR). FIG. 2A: full-length AR amino acid sequence; FIG. 2B-2I: amino acid sequences of LBD of AR. (SEQ ID NOs:85-93).

FIG. 3A-3D depict amino acid sequences of progesterone receptors (PR). FIG. 3A: full-length PR amino acid sequence; FIG. 3B-3C: amino acid sequences of LBD of PR; FIG. 3D: multiple sequence alignment of LBD of PR of various species. (SEQ ID NOs:94-103).

FIG. 4A-4D depict amino acid sequences of thyroid hormone receptor-beta (TRβ). FIG. 3A: full-length PR amino acid sequence; FIG. 3B-3C: amino acid sequences of LBD of TRβ; FIG. 3D: multiple sequence alignment of LBD of TRβ of various species. (SEQ ID NO:104-118).

FIG. 5A-5H depict amino acid sequences of estrogen receptor-alpha (ERα). FIG. 5A: full-length ERα amino acid sequence; FIG. 5B-5G: amino acid sequences of LBD of ERα; FIG. 5H; multiple sequence alignment of LBD of ERα of various species. (SEQ ID NO:119-133).

FIG. 6A-6C depict amino acid sequences of estrogen receptor-beta (ERβ). FIG. 6A: full-length ERβ amino acid sequence; FIG. 6B: amino acid sequence of LBD of ERβ; FIG. 6C; multiple sequence alignment of LBD of ERβ of various species. (SEQ ID NO:134-143).

CLAIMS

What is claimed is:

1. A heterodimeric, conditionally active polypeptide comprising:

a) a first chimeric polypeptide comprising a first member of a dimerization pair and a first heterologous polypeptide; and

b) a second chimeric polypeptide comprising a second member of a dimerization pair and a second heterologous polypeptide,

wherein the first member of the dimerization pair comprises a ligand-binding domain (LBD) of a nuclear hormone receptor, and the second member of the dimerization pair comprises a co-regulator of the nuclear hormone receptor, or

wherein the first member of the dimerization pair is a co-regulator of a nuclear hormone receptor, and the second member of the dimerization pair comprises an LBD of the nuclear hormone receptor; and

wherein the first chimeric polypeptide and the second chimeric polypeptide are dimerized in the presence of a dimerization agent that induces binding of the LBD to the co-regulator.

2. The heterodimeric, conditionally active polypeptide of claim 1, wherein:

a) the first heterologous polypeptide is a T-cell receptor (TCR) alpha chain and b) the second heterologous polypeptide is a TCR beta chain;

a) the first heterologous polypeptide is a first polypeptide of a chimeric antigen receptor (CAR) heterodimer and b) the second heterologous polypeptide is a second polypeptide of a CAR heterodimer;

a) the first heterologous polypeptide is an N-terminal portion of an enzyme and b) the second heterologous polypeptide is a C-terminal portion of the enzyme, wherein dimerization of the first chimeric polypeptide and the second chimeric polypeptide restore enzymatic activity of the enzyme; or

a) the first heterologous polypeptide is an N-terminal portion of a receptor and b) the second heterologous polypeptide is a C-terminal portion of the receptor, wherein dimerization of the first chimeric polypeptide and the second chimeric polypeptide mediated by the dimerization agent restores signaling activity of the receptor.

3. The heterodimeric, conditionally active polypeptide of any one of claims 1-2, wherein LBD of the nuclear hormone binding member of the dimerization pair is an LBD of a nuclear hormone receptor selected from an estrogen receptor, an ecdysone receptor, a PPARγ receptor, a glucocorticoid receptor, an androgen receptor, a thyroid hormone receptor, a mineralocorticoid receptor, a progesterone

receptor, a vitamin D receptor, a PPARβ receptor, a PPARα receptor, a pregnane X receptor, a liver X receptor, a farnesoid X receptor, a retinoid X receptor, a RAR-related orphan receptor, and a retinoic acid receptor.

4. The heterodimeric, conditionally active polypeptide of any one of claims 1-3, wherein the co-regulator of the nuclear hormone receptor is selected from SRC1, GRIP1, AIB1, PGC1a, PGC1b, PRC, TRAP220, ASC2, CBP, P300, CIA, ARA70, TIF1, NSD1, SMAP, Tip60, ERAP140, Nix1, LCoR, N-CoR, SMRT, RIP140, and PRIC285.

5. The heterodimeric, conditionally active polypeptide of any one of claims 1-4, wherein the co-regulator of the nuclear hormone receptor is selected from:

a) SRC1: CPSSHSSLTERHKILHRLLQEGSPS (SEQ ID NO:1);

b) SRC1–2: SLTARHKILHRLLQEGSPSDI (SEQ ID NO:2);

c) SRC3-1: ESKGHKKLLQLLTCSSDDR (SEQ ID NO:3);

d) SRC3: PKKENNALLRYLLDRDDPSDV (SEQ ID NO:4);

e) PGC-1: AEEPSLLKKLLLAPANT (SEQ ID NO:5);

f) PGC1a: QEAEEPSLLKKLLLAPANTQL (SEQ ID NO:6);

g) TRAP220–1: SKVSQNPILTSLLQITGNGGS (SEQ ID NO:7);

h) NCoR (2051–2075): GHSFADPASNLGLEDIIRKALMGSF (SEQ ID NO:8);

i) NR0B1: PRQGSILYSMLTSAKQT (SEQ ID NO:9);

j) NRIP1: AANNSLLLHLLKSQTIP (SEQ ID NO:10);

k) TIF2: PKKKENALLRYLLDKDDTKDI (SEQ ID NO:11);

l) CoRNR Box: DAFQLRQLILRGLQDD (SEQ ID NO:12);

m) αβV: SPGSREWFKDMLS (SEQ ID NO:13);

n) TRAP220-2: GNTKNHPMLMNLLKDNPAQDF (SEQ ID NO:14);

o) EA2: SSKGVLWRMLAEPVSR (SEQ ID NO:15);

p) TA1: SRTLQLDWGTLYWSR (SEQ ID NO:16);

q) EAB1: SSNHQSSRLIELLSR (SEQ ID NO:17);

r) SRC2: LKEKHKILHRLLQDSSSPV (SEQ ID NO:18);

s) SRC1-3: QAQQKSLLQQLLTE (SEQ ID NO:19);

t) SRC1–1: KYSQTSHKLVQLLTTTAEQQL (SEQ ID NO:20);

u) SRC1–2: SLTARHKILHRLLQEGSPSDI (SEQ ID NO:21);

v) SRC1–3: KESKDHQLLRYLLDKDEKDLR (SEQ ID NO:22);

w) SRC1–4a: PQAQQKSLLQQLLTE (SEQ ID NO:23);;

x) SRC1–4b: PQAQQKSLRQQLLTE (SEQ ID NO:24);

y) GRIP1–1: HDSKGQTKLLQLLTTKSDQME (SEQ ID NO:25);

z) GRIP1–2: SLKEKHKILHRLLQDSSSPVD (SEQ ID NO:26);

aa) GRIP1–3: PKKKENALLRYLLDKDDTKDI (SEQ ID NO:27);

bb) AIB1–1: LESKGHKKLLQLLTCSSDDRG (SEQ ID NO:28);

cc) AIB1–2: LLQEKHRILHKLLQNGNSPAE (SEQ ID NO:29);

dd) AIB1–3: KKKENNALLRYLLDRDDPSDA (SEQ ID NO:30);

ee) PGC1a: QEAEEPSLLKKLLLAPANTQL (SEQ ID NO:31);

ff) PGC1b: PEVDELSLLQKLLLATSYPTS (SEQ ID NO:32);

gg) PRC: VSPREGSSLHKLLTLSRTPPE (SEQ ID NO:33);

hh) TRAP220–1: SKVSQNPILTSLLQITGNGGS (SEQ ID NO:34);

ii) TRAP220–2: GNTKNHPMLMNLLKDNPAQDF (SEQ ID NO:35);

jj) ASC2–1: DVTLTSPLLVNLLQSDISAGH (SEQ ID NO:36);

kk) ASC2–2: AMREAPTSLSQLLDNSGAPNV (SEQ ID NO:37);

ll) CBP-1: DAASKHKQLSELLRGGSGSSI (SEQ ID NO:38);

mm) CBP-2: KRKLIQQQLVLLLHAHKCQRR (SEQ ID NO:39);

nn) P300: DAASKHKQLSELLRSGSSPNL (SEQ ID NO:40);

oo) CIA: GHPPAIQSLINLLADNRYLTA (SEQ ID NO:41);

pp) ARA70–1: TLQQQAQQLYSLLGQFNCLTH (SEQ ID NO:42);

qq) ARA70–2: GSRETSEKFKLLFQSYNVNDW (SEQ ID NO:43);

rr) TIF1: NANYPRSILTSLLLNSSQSST (SEQ ID NO:44);

ss) NSD1: IPIEPDYKFSTLLMMLKDMHD (SEQ ID NO:45);

tt) SMAP: ATPPPSPLLSELLKKGSLLPT (SEQ ID NO:46);

uu) Tip60: VDGHERAMLKRLLRIDSKCLH (SEQ ID NO:47);

vv) ERAP140: HEDLDKVKLIEYYLTKNKEGP (SEQ ID NO:48);

ww) Nix1: ESPEFCLGLQTLLSLKCCIDL (SEQ ID NO:49);

xx) LCoR: AATTQNPVLSKLLMADQDSPL (SEQ ID NO:50);

yy) CoRNR1 (N-CoR): MGQVPRTHRLITLADHICQIITQDFARNQV (SEQ ID NO:51);

zz) CoRNR2 (N-CoR): NLGLEDIIRKALMG (SEQ ID NO:52);

aaa) CoRNR1 (SMRT): APGVKGHQRVVTLAQHISEVITQDTYRHHPQQLSAPLPAP (SEQ ID NO:53);

bbb) CoRNR2 (SMRT): NMGLEAIIRKALMG (SEQ ID NO:54);

ccc) RIP140-C: RLTKTNPILYYMLQKGGNSVA (SEQ ID NO:55);

ddd) RIP140-1: QDSIVLTYLEGLLMHQAAGGS (SEQ ID NO:56);

eee) RIP140-2: KGKQDSTLLASLLQSFSSRLQ (SEQ ID NO:57);

fff) RIP140-3: CYGVASSHLKTLLKKSKVKDQ (SEQ ID NO:58);

ggg) RIP140-4: KPSVACSQLALLLSSEAHLQQ (SEQ ID NO:59);

hhh) RIP140-5: KQAANNSLLLHLLKSQTIPKP (SEQ ID NO:60);

iii) RIP140-6: NSHQKVTLLQLLLGHKNEENV (SEQ ID NO:61);

jjj) RIP140-7: NLLERRTVLQLLLGNPTKGRV (SEQ ID NO:62);

kkk) RIP140-8: FSFSKNGLLSRLLRQNQDSYL (SEQ ID NO:63);

lll) RIP140-9: RESKSFNVLKQLLLSENCVRD (SEQ ID NO:64);

mmm) PRIC285-1: ELNADDAILRELLDESQKVMV (SEQ ID NO:65);

nnn) PRIC285-2: YENLPPAALRKLLRAEPERYR (SEQ ID NO:66);

ooo) PRIC285-3: MAFAGDEVLVQLLSGDKAPEG (SEQ ID NO:67);

ppp) PRIC285-4: SCCYLCIRLEGLLAPTASPRP (SEQ ID NO:68); and

qqq) PRIC285-5: PSNKSVDVLAGLLLRRMELKP (SEQ ID NO:69).

6. A heterodimeric, conditionally active receptor comprising:

a) a first chimeric polypeptide comprising:

i) a first member of a specific binding pair;

ii) a first modulatory domain;

iii) a first member of a dimerization pair; and

iv) a transmembrane domain interposed between the first member of a specific binding pair and the first modulatory domain; and

b) a second chimeric polypeptide comprising:

i) a transmembrane domain;

ii) a second modulatory domain;

iii) a second member of the dimerization pair; and

iv) an intracellular signaling domain;

or comprising:

a) a first chimeric polypeptide comprising:

i) a first member of a specific binding pair;

ii) a modulatory domain;

iii) a first member of a dimerization pair;

iv) a transmembrane domain interposed between the first member of a specific binding pair and the modulatory domain; and

b) a second chimeric polypeptide comprising:

i) a second member of the dimerization pair; and

ii) an intracellular signaling domain.

wherein the first member of the dimerization pair comprises a ligand-binding domain (LBD) of a nuclear hormone receptor, and the second member of the dimerization pair comprises a co-regulator of the nuclear hormone receptor, or

wherein the first member of the dimerization pair is a co-regulator of a nuclear hormone receptor, and the second member of the dimerization pair comprises an LBD of the nuclear hormone receptor,

wherein the first chimeric polypeptide and the second chimeric polypeptide are dimerized in the presence of a dimerization agent that induces binding of the LBD to the co-regulator.

7. A heterodimeric, conditionally repressible synthetic immune cell receptor (ICR) comprising:

a synthetic stimulatory ICR comprising a first member of a dimerization pair linked to the synthetic stimulatory ICR; and

a synthetic ICR repressor comprising a second member of the dimerization pair linked to an intracellular inhibitory domain,

wherein the first member of the dimerization pair comprises a ligand-binding domain (LBD) of a nuclear hormone receptor, and the second member of the dimerization pair comprises a co-regulator of the nuclear hormone receptor, or

wherein the first member of the dimerization pair is a co-regulator of a nuclear hormone receptor, and the second member of the dimerization pair comprises an LBD of the nuclear hormone receptor,

wherein the synthetic stimulatory ICR and the synthetic ICR repressor are dimerized in the presence of a dimerization agent that induces binding of the LBD to the co-regulator.

8. The conditionally repressible synthetic ICR of Claim 7, wherein the synthetic stimulatory ICR comprises an intracellular co-stimulatory domain, optionally wherein the intracellular co-stimulatory domain is selected from the group consisting of: 4-1BB (CD137), CD28, ICOS, OX-40, BTLA, CD27, CD30, GITR, and HVEM.

9. The conditionally repressible synthetic ICR of any one claims 7-8, wherein the intracellular inhibitory domain is an inhibitory domain derived from a protein selected from the group consisting of: PD-1, CTLA4, HPK1, SHP1, SHP2, Sts1 and Csk.

10. A heterodimeric, conditionally repressible synthetic chimeric antigen receptor (CAR) comprising:

a) a synthetic stimulatory CAR comprising:

i) an extracellular recognition domain;

ii) a transmembrane domain linked to the extracellular recognition domain;

iii) a first member of a dimerization pair linked to the transmembrane domain; and

iv) an intracellular stimulation domain; and

b) a synthetic CAR repressor comprising:

i) a second member of the dimerization pair; and

ii) an intracellular inhibitory domain linked to the second member of the dimerization pair,

wherein the first member of the dimerization pair comprises a ligand-binding domain (LBD) of a nuclear hormone receptor, and the second member of the dimerization pair comprises a co-regulator of the nuclear hormone receptor, or

wherein the first member of the dimerization pair is a co-regulator of a nuclear hormone receptor, and the second member of the dimerization pair comprises an LBD of the nuclear hormone receptor; and

wherein the synthetic stimulatory CAR and the synthetic CAR repressor are dimerized in the presence of a dimerization agent that induces binding of the LBD to the co-regulator.

11. A heterodimeric, conditionally repressible synthetic T cell receptor (TCR) comprising:

a) a synthetic stimulatory TCR comprising:

i) a transmembrane domain;

ii) a first member of a dimerization pair linked to the transmembrane domain;

iii) an engineered TCR polypeptide comprising at least one TCR alpha or beta chain, wherein the at least one TCR alpha or beta chain is linked to the transmembrane domain or the first member of a dimerization pair; and

b) a synthetic TCR repressor comprising:

i) a second member of the dimerization pair; and

ii) an intracellular inhibitory domain linked to the second member of the dimerization pair,

wherein the first member of the dimerization pair comprises a ligand-binding domain (LBD) of a nuclear hormone receptor, and the second member of the dimerization pair comprises a co-regulator of the nuclear hormone receptor, or

wherein the first member of the dimerization pair is a co-regulator of a nuclear hormone receptor, and the second member of the dimerization pair comprises an LBD of the nuclear hormone receptor; and

wherein the synthetic stimulatory TCR and the synthetic TCR repressor are dimerized in the presence of a dimerization agent that induces binding of the LBD to the co-regulator.

12. A heterodimeric, conditionally active chimeric antigen receptor (CAR) comprising:

a) a first polypeptide comprising:

i) a first member of a specific binding pair;

ii) a first modulatory domain;

iii) a first member of a dimerization pair; and

iv) a transmembrane domain interposed between the first member of a specific binding pair and the first modulatory domain; and

b) a second polypeptide comprising:

i) a transmembrane domain;

ii) a second modulatory domain;

iii) a second member of the dimerization pair; and

iv) an intracellular signaling domain;

or comprising:

a) a first polypeptide comprising:

i) a first member of a specific binding pair;

ii) a modulatory domain;

iii) a first member of a dimerization pair;

iv) a transmembrane domain interposed between the first member of a specific binding pair and the modulatory domain; and

b) a second polypeptide comprising:

i) a second member of the dimerization pair; and

ii) an intracellular signaling domain,

wherein the first member of the dimerization pair comprises a ligand-binding domain (LBD) of a nuclear hormone receptor, and the second member of the dimerization pair comprises a co-regulator of the nuclear hormone receptor, or

wherein the first member of the dimerization pair is a co-regulator of a nuclear hormone receptor, and the second member of the dimerization pair comprises an LBD of the nuclear hormone receptor; and

wherein the first polypeptide and the second polypeptide are dimerized in the presence of a dimerization agent that induces binding of the LBD to the co-regulator.

13. The heterodimeric, conditionally active CAR of claim 12, wherein the first and second modulatory domains are selected from 4-1BB (CD137), CD28, ICOS, BTLA, OX-40, CD27, CD30, GITR, HVEM, DAP10, DAP12, and CD28.

14. The heterodimeric, conditionally active CAR of any of claims 12-13, wherein the intracellular signaling domain comprises an immunoreceptor tyrosine-based activation motif (ITAM).

15. The heterodimeric, conditionally active CAR of any of claims 12-14, wherein the first member of the specific binding pair binds an epitope present on a cell and the cell is a cancer cell.

16. A mammalian cell genetically modified to produce the heterodimeric, conditionally active polypeptide or receptor of any one of claims 1-15.

17. A nucleic acid comprising nucleotide sequences encoding the heterodimeric, conditionally active receptor or polypeptide of any one of claims 1-15.

18. A method of modulating an activity of a eukaryotic cell, the method comprising:

a) expressing the heterodimeric, conditionally active polypeptide or receptor of any one of claims 1-15 in the eukaryotic cell; and

b) contacting the cell with the ligand.

19. A method of making the cell of claim 16, the method comprising genetically modifying a mammalian cell with an expression vector comprising nucleotide sequences encoding the heterodimeric, conditionally active receptor or polypeptide of any one of claims 1-15, or genetically modifying a mammalian cell with an RNA comprising nucleotide sequences encoding the heterodimeric, conditionally active receptor or polypeptide of any one of claims 1-15.

20. Use of an expression vector comprising nucleotide sequences encoding the heterodimeric, conditionally active chimeric antigen receptor (CAR) of claim 15 in the manufacture of a medicament for treating a cancer in an individual, wherein:

i) T lymphocytes obtained from the individual are to be genetically modified with the medicament, wherein the antigen-binding domain of the heterodimeric, conditionally active CAR is

specific for an epitope on a cancer cell in the individual, and wherein said genetic modification is to be carried out ex vivo;

ii) the genetically modified T lymphocytes are to be introduced into the individual; and

iii) an effective amount of a dimerizing agent is to be administered to the individual, wherein the dimerizing agent induces dimerization of the heterodimeric, conditionally active receptor, wherein said dimerization provides for activation of the genetically modified T lymphocytes and killing of the cancer cell, thereby treating the cancer.