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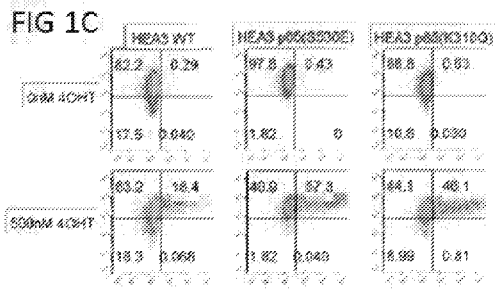
(54) Title: CHIMERIC TRANSCRIPTION FACTOR VARIANTS WITH AUGMENTED SENSITIVITY TO DRUG LIGAND INDUCTION OF TRANSGENE EXPRESSION IN MAMMALIAN CELLS

FIG 1C



(57) Abstract: Provided herein is a system for inducible expression of a chimeric antigen receptor in cells. The system comprises: a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain, a second polynucleotide, which encodes a spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain, and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by drug. Methods of making such cells and methods of treatment using these cells are also provided.

CHIMERIC TRANSCRIPTION FACTOR VARIANTS WITH AUGMENTED SENSITIVITY TO DRUG LIGAND INDUCTION OF TRANSGENE EXPRESSION IN MAMMALIAN CELLS

INCORPORATION BY REFERENCE TO A PRIORITY APPLICATION

[0001] The present application claims the benefit of priority to U.S. Provisional Patent Application No. 62/433,183, filed December 12, 2016. The entire disclosure of the aforementioned application is hereby expressly incorporated by reference in its entirety.

REFERENCE TO SEQUENCE LISTING, TABLE, OR COMPUTER PROGRAM LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled SCRI.118WO.txt, created December 6, 2017, which is 297 kb in size. The information provided is the electronic format of the Sequence Listing and is hereby expressly incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0003] Disclosed herein are embodiments relating to genetic systems that facilitate drug-regulated transgene expression in cells, for instance mammalian cells. The present disclosure also concerns the identification of variants of the wild-type HEA3 and wild-type HEA4 chimeric transcription factors, which are useful for the regulation of transgene expression in genetically modified cells including mammalian cells.

BACKGROUND

[0004] Human T lymphocytes can be engineered by gene transfer to express chimeric antigen receptors (CARs), which are specific for surface molecules expressed on tumor cells. Methods of gene transfer useful for this purpose include several types of viral transduction using viral vectors encoding the chimeric antigen receptors. Cells expressing the chimeric antigen receptors can then be adoptively transferred to patients to treat cancer and infectious diseases. Chimeric antigen receptors are synthetic receptors. These synthetic

receptors, can include an extracellular ligand binding domain, for example, a single chain variable fragment of a monoclonal antibody (scFv) linked to intracellular signaling components, such as CD3ζ alone or combined with one or more costimulatory domains. Research in the design of chimeric receptors has focused on defining scFvs and other ligand binding elements that target malignant cells without causing severe toxicity to normal tissues, and on defining the optimal composition of intracellular signaling modules to activate T cell effector functions. Additional genetic systems that facilitate expression of chimeric antigen receptors are needed.

SUMMARY OF THE INVENTION

[0005] Aspects of the present invention concern genetic systems that facilitate drug-regulated transgene expression in cells. In one alternative, regulated transgene expression is targeted to cells, such as lymphocytes, preferably human lymphocytes, which are designed for use in adoptive immunotherapy. This system provides rigorous safety attributes to chimeric antigen receptor (CAR) redirected adoptive therapeutic strategies without sacrificing curative intent that permits real-time clinician control of CAR expression *in vivo*. By engineering vectors that enable drug responsive transcriptional control of CAR expression, the activity of CARs and other cell mediators can be turned "ON" and "OFF" *in vivo,* based on a clinician prescribed pharmaceutical drug input that exhibits clinically permissive pharmacokinetics, tissue distribution, and partitioning between the extracellular space and cytosol of lymphocytes. In addition to adenovirus and lentivirus genes, the vector platform can also include genes encoding minicircles or piggy bac transposons. The genetic systems described herein provide for drug regulated transgene expression to enforce a functional "OFF" state in the absence of the drug and a functional "ON" state transgene expression in the presence of the drug.

[0006] One alternative of such an approach utilizes the drug tamoxifen. Tamoxifen is an estrogen antagonist/partial agonist that is an FDA-approved and commercially available drug. It is taken orally and can be administered daily and over an extended period. Tamoxifen has a proven safety record, favorable pharmacokinetic profile, excellent tissue distribution and a low partition coefficient between the extracellular space and cytosol. Other drugs useful in the approaches described herein can be selected based on

safety record, favorable pharmacokinetic profile, and excellent tissue distribution, a low partition coefficient between the extracellular space and cytosol, and/or low toxicities.

[0007] Tamoxifen can have several side effects, however, such as cataracts, changes in menstrual period, constipation, diarrhea, edema (swelling), fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting and weight loss, for example. As such, it is necessary to turn on a gene for expressing the chimeric antigen receptor at a low plasma concentration of tamoxifen for some patients.

[0008] One aspect of the disclosure relates to changes that can be made to transcriptional activators so as to modulate the properties of the transcription factors including, without limitation, altering one or more amino acids in the estrogen receptor ligand binding domain so as to increase the affinity of the factor for estrogen analogs and altering one or more amino acids in the p65 transactivating domain and/or the RelA (p65) transactivation domain, in which altering the amino acids in the p65 transactivating domain (RelA) can enhance the transcriptional activity in response to a drug. The RelA mutations enhance transcriptional activity in response to the drug, however, they do not affect drug-to-receptor binding. Only the mutations in the ER-LBD affect drug-to-receptor binding. In some alternatives, the system employs a synthetic transcriptional regulator, which, in the presence of tamoxifen, binds a synthetic promoter upstream of a transgene to induce expression. The tamoxifen regulated transcription factors ("TamR-tf", also can refer to HEA3/HEA4 transcription factors) is a chimeric transcription factor composed of human subunits including the N-terminal DNA binding domain of Hepatocyte Nuclear Factor 1-alpha (HNF-1α) fused in frame to the mutant tamoxifen-specific ligand binding domain of the estrogen receptor ligand binding domain (ER-LBD), that is in turn fused to the p65 activation domain of NF-κB (p65). HEA4 is a chimeric transcription factor composed of human subunits including the N-terminal DNA binding domain of Hepatocyte Nuclear Factor 1-alpha (HNF-1α) fused in frame to the mutant tamoxifen-specific ligand binding domain of the estrogen receptor ligand binding domain (ER-LBD) containing three point mutations (G400V, M543A, L544A) that abolish estradiol binding but permit binding to tamoxifen metabolites and other estrogen analogues, that is in turn fused to the p65 activation domain of NF-κB (p65). An exemplary amino acid sequence is set forth in SEQ ID NO: 1

(MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FKSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADM
DFSALLSQISS). SEQ ID NO: 1 comprises one point mutation in the ER-LBD that ablates binding to endogenous estrogen, but confers nanomolar specificity to tamoxifen metabolite 4-OHT fulvestrant and other estrogen analogs. The mutant tamoxifen-specific ligand binding domain of the estrogen receptor ligand binding domain (ER-LBD) is found at amino acids 282-595 of the TamR-tf and has a mutation at position 521 (G521R), and affects drug-to-receptor binding. The p65 activation domain of NF-κB (p65) is found at amino acids 596-862 of SEQ ID NO: 1 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA

QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FKSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADM
DFSALLSQISS).

[0009] In the absence of tamoxifen, TamR-tf is excluded from the nucleus by binding of cytosolic heat-shock protein 90 (HSP90) to the tamoxifen binding active site and transgene expression is in the "OFF" state. Nanomolar concentrations of cytosolic tamoxifen actively out compete HSP90 for ER-LBD binding, resulting in TamR-tf translocation to the nucleus. Upon nuclear translocation, TamR-tf is readily available to bind its restricted synthetic promoter (e.g. 7xHBD/mE1B as set forth in the nucleic acid sequence of SEQ ID NO: 23 (tagttaataatctacaatagttaataatctacaatagttaataatctacaatagttaataatctacaatagttaataatctacaatagttaataatctacaatagttaataatctacaagagctcagggtatataatg). In the presence of tamoxifen, binding of TamR-tf to 7xHBD/mE1B promoter induces the "ON" state of transgene expression. In some alternatives, this transcriptional regulator can be modified to provide for a varying level of control of transgene expression. Amino acid substitutions in the LBD of TamR-tf permit selective responsiveness to tamoxifen and its metabolites, which affect the drug-to-receptor binding, where 4-hydroxy tamoxifen (4-OHT) is the most pharmacologically active metabolite, with respect to TamR-tf activity, while lacking interaction with endogenous estrogen.

[0010] In some alternatives, variants of wild-type HEA3 and wild-type HEA4 are identified with augmented sensitivity to a drug by virtue of substitutions of the human estrogen receptor ligand binding domain. Mutations in the RelA (p65) transactivation domain augment transcriptional activity in response to drug or drug ligand. In some alternatives, these high affinity forms are generated by amino acid substitutions within the human estrogen receptor that confer selective binding to 4-OHT and other estrogen analogs such as fulvestrant. These changes cooperatively enhance transgene expression in response to drug activators when combined with amino acid substitutions in the HEA3 and HEA4 RelA

domain that function as phosphomimetics and acetyl-mimetics, for example. Also described herein is a preferred version of the variant housing all three modifications that does not adversely affect the stringency of the "OFF" state in the absence of ligand, but dramatically improves the sensitivity and magnitude of transgene expression to activating estrogen analogue drug inputs. In another aspect, HEA3 is rendered responsive to the drug CMP8 due to mutations in the ER-LBD (L384M, M421G, G521R), not RelA mutations. The RelA mutations may not affect specificity to drug. The RelA mutations may enhance transcriptional activity. These enhanced HEA3 and HEA4 chimeric transcription factors make this regulatory system responsive to input drug levels that can easily be reached with low dose non-toxic dosing of tamoxifen, fulvestrant, or CMP8.

[0011] In a first aspect, a system for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, is provided. The system comprises: a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral specific molecule, and any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a second polynucleotide, which encodes a polypeptide spacer, preferably an optimized spacer; a third polynucleotide, which encodes a transmembrane domain; and a fourth polynucleotide, which encodes an intracellular signaling domain; and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter, which is inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug as compared to a wild type HEA3 chimeric transcription factor. In some alternatives, the transcriptional activator for the first promoter inducible by a drug, is HEA3 or HEA4. In some alternatives, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain

comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives, the at least one mutation affects the drug-to-receptor binding. In some alternatives, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional expression at a given concentration compared to a system using a wild type HEA3. In some alternatives, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives, the variant of the wild type HEA3 transcription factor comprises at least one or more amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and 121. In some alternatives, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or at a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives, the non-toxic

dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 chimeric transcription factor. In some alternatives, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives, the second promoter is an inducible promoter. In some alternatives, the second promoter is a constitutive promoter. In some alternatives, the second promoter is the EF1αp. In some alternatives, the transcriptional activator comprises at least one or more amino acid sequences set forth in SEQ ID NO: 1-11 or 121. In some alternatives, the transcriptional activator is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12-22 or 122. In some alternatives, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives, both vectors are packaged in a viral vector. In some alternatives, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives, the selectable marker is EGFRt and/or HER2t. In some alternatives, the selectable marker confers drug resistance. In some alternatives, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand, as compared to a reference chimeric receptor. In some alternatives, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives, the drug induces expression of the chimeric antigen receptor at a

non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives, the second nucleic acid further comprises a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral specific molecule, or any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is preferably optimized, a polynucleotide coding for a transmembrane domain and a polynucleotide encoding an intracellular signaling domain. In some alternatives, the first promoter is in opposite orientation to the second promoter. In some alternatives, the ligand binding domain is an antibody fragment, such as a binding fragment. In some alternatives, the ligand binding domain is a single chain variable fragment. In some alternatives, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combinations thereof. In some alternatives, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, and/or Epstein-Barr virus early antigen protein. In some alternatives, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives, the spacer comprises IgG4, IgG4-CH2 (L235D, N297Q) or IgG4-CH3. In some alternatives, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in

between a range defined by any two aforementioned values. In some alternatives, the DNA spacer enhances gene expression of the chimeric antigen receptor.

[0012] In a second aspect, a system for inducible expression of a gene that regulates a T cell function is provided. The system comprises: a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity, and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter, which is inducible by a drug and, wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a wild type HEA3. In some alternatives, the transcriptional activator is HEA3 or HEA4. In some alternatives, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives, HEA3 or HEA4 chimeric transcription factor comprises p65

phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives, the variant of a wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3 and/or 8-11 and/or 121. In some alternatives, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 and/or 122. In some alternatives, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives, the second nucleic acid further comprises a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a polynucleotide coding for a polypeptide spacer, wherein the spacer is preferably optimized, a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives, the first promoter is in opposite orientation to the

second promoter. In some alternatives, the ligand binding domain is an antibody fragment, such as a binding fragment. In some alternatives, the ligand binding domain is a single chain variable fragment. In some alternatives, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combinations thereof. In some alternatives, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives, the spacer comprises IgG4, IgG4-CH2 (L235D, N297Q) or IgG4-CH3. In some alternatives, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives, both vectors are packaged in a viral vector. In some alternatives, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the polypeptide that regulates apoptosis is Survivin. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124. In some alternatives, Survivin comprises an amino acid sequence set forth in SEQ ID NO: 123.

[0013] In a third aspect, a chimeric receptor polypeptide coded for by the first second and/or second nucleic acid of the system of any one of the alternative systems described herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, the

system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from a tumor specific molecule, a viral molecule, or other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a polypeptide spacer, preferably an optimized spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible

expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 and/or. 122In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 and/or 18. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the non-toxic dosing

of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is an inducible promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is a constitutive promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is the EF1αp. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator comprises at least one or more amino acid sequences set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, both vectors are packaged in a viral vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker is EGFRt and/or HER2t. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker confers drug resistance. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the

first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives, the system is a system for inducible expression of a gene that regulates a T cell function. In some alternatives, the system for inducible expression of a gene that regulates a T cell function comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least

one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the systems described herein, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the systems described herein, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the systems described herein, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500

nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the systems described herein, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the systems described herein, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the systems described herein, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the systems described herein, the second nucleic acid further comprises a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral specific molecule, or any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a polynucleotide coding for a polypeptide spacer, wherein the spacer is preferably optimized, a polynucleotide coding for a transmembrane domain, and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the systems described herein, the first promoter is in opposite orientation to the second promoter. In some alternatives of the systems described herein, the ligand binding domain is an antibody fragment. In some alternatives of the systems described herein, the ligand binding domain is a single chain variable fragment. In some alternatives of the systems described herein, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or combinations thereof. In some alternatives of the systems described herein, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives, the spacer comprises IgG4, IgG4-CH2 (L235D, N297Q) or IgG4-CH3. In some alternatives of the systems described herein, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked

to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the systems described herein, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the systems described herein, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the systems described herein, both vectors are packaged in a viral vector. In some alternatives of the systems described herein, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the polypeptide that regulates apoptosis is Survivin. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124. In some alternatives, Survivin comprises an amino acid sequence set forth in SEQ ID NO: 123.

[0014] In a fourth aspect, a host cell comprising a system of any one of the alternative systems described herein is provided. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells the system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from a tumor specific molecule, a viral molecule, or other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by drug, wherein the system is inducible by an amount of the drug

that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3 8-11 and/or. 121 In some alternatives of the system for inducible expression of a chimeric antigen

receptor in cells, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is an inducible promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is a

constitutive promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is the EF1αp. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator comprises at least one or more amino acid sequences set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, both vectors are packaged in a viral vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker is EGFRt and/or HER2t. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker confers drug resistance. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. In some alternatives, the system for inducible expression of a gene that regulates a T cell function comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a

chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the HEA3 or

HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and 121. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 and/or 18. In some alternatives of the systems described herein, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the systems described herein, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the systems described herein, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the systems described herein, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the systems described herein, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the systems described herein, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the systems described herein, the second nucleic acid further comprises a

polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized, a polynucleotide coding for a transmembrane domain, and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the systems described herein, the first promoter is in opposite orientation to the second promoter. In some alternatives of the systems described herein, the ligand binding domain is an antibody fragment. In some alternatives of the systems described herein, the ligand binding domain is a single chain variable fragment. In some alternatives of the systems described herein, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR and/or combinations thereof. In some alternatives of the systems described herein, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the systems described herein, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the systems described herein, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the systems described herein, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the systems described herein, both vectors are packaged in a viral vector. In some alternatives of the systems described herein, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the host cell, the host cell is a mammalian cell, such as a precursor T cell. In some alternatives of the

host cell, the precursor T cell is a hematopoietic stem cell. In some alternatives of the host cell, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives of the host cell, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives, the spacer comprises IgG4, IgG4-CH2 (L235D, N297Q) or IgG4-CH3. In some alternatives, the polypeptide that regulates apoptosis is Survivin. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124. In some alternatives, Survivin comprises an amino acid sequence set forth in SEQ ID NO: 123.

[0015] In a fifth aspect, a composition comprising a host cell of any one or more of alternative host cells, such as mammalian cells, provided herein, in a pharmaceutically acceptable excipient, is provided. The host cell, such as a mammalian cell, comprises a system of any one of the alternative systems described herein is provided. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, , such as mammalian cells ,the system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from a tumor specific molecule, a viral molecule, or other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription

factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor is encoded by at least

one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is an inducible promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is a constitutive promoter. In some alternatives of the system for inducible expression of a

chimeric antigen receptor in cells, the second promoter is the EF1αp. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator comprises at least one or more amino acid sequences set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, both vectors are packaged in a viral vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker is EGFRt and/or HER2t. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker confers drug resistance. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a

polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic

amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the systems described herein, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the systems described herein, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the systems described herein, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or a wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the systems described herein, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the systems described herein, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the systems described herein, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the systems described herein, the second nucleic acid further comprises a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain,

which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized, a polynucleotide coding for a transmembrane domain, and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the systems described herein, the first promoter is in opposite orientation to the second promoter. In some alternatives of the systems described herein, the ligand binding domain is an antibody fragment. In some alternatives of the systems described herein, the ligand binding domain is a single chain variable fragment. In some alternatives of the systems described herein, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR and/or any combinations thereof. In some alternatives of the systems described herein, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the host cell, the host cell is a precursor T cell. In some alternatives of the systems described herein, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the systems described herein, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the systems described herein, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the systems described herein, both vectors are packaged in a viral vector. In some alternatives of the systems described herein, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the host cell, such as a mammalian cell, the cell is a precursor T cell, which can be a hematopoietic stem cell. In

some alternatives of the host cell, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives of the host cell, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives of the composition, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells and a host cell, wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives of the composition, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells or wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells and a host cell wherein the host cell is a precursor T cell or a hematopoietic stem cell. In some alternatives, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives, the spacer comprises IgG4, IgG4-CH2 (L235D, N297Q) or IgG4-CH3. In some alternatives, the polypeptide that regulates apoptosis is Survivin. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124. In some alternatives, Survivin comprises an amino acid sequence set forth in SEQ ID NO: 123.

[0016] In a sixth aspect, an *in vitro* method for preparing a host cell of any one of the alternative host cells, such as mammalian cells, described herein is provided. The host cell, such as a mammalian cell, comprises a system of any one of the alternative systems described herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, the system comprises a) a first nucleic acid comprising a first promoter inducible by a drug,

wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from a tumor specific molecule, a viral specific molecule, or any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells,

HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the non-toxic dosing of drug decreases, eliminates or

prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is an inducible promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is a constitutive promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is the EF1αp. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator comprises at least one or more amino acid sequences set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, both vectors are packaged in a viral vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker is EGFRt and/or HER2t. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker confers drug resistance. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the

first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least

one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the systems described herein, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the systems described herein, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the systems described herein, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or a wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500

nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the systems described herein, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the systems described herein, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the systems described herein, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the systems described herein, the second nucleic acid further comprises a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral specific molecule, or any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a polynucleotide coding for a polypeptide spacer, wherein the spacer is preferably optimized, a polynucleotide coding for a transmembrane domain, and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the systems described herein, the first promoter is in opposite orientation to the second promoter. In some alternatives of the systems described herein, the ligand binding domain is an antibody fragment, such as a binding fragment. In some alternatives of the systems described herein, the ligand binding domain is a single chain variable fragment. In some alternatives of the systems described herein, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR and/or any combinations thereof. In some alternatives of the systems described herein, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the host cell, the host cell is a mammalian cell, such as a precursor T cell. In some alternatives of the systems described herein, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer is between the first

promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the systems described herein, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the systems described herein, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the systems described herein, both vectors are packaged in a viral vector. In some alternatives of the systems described herein, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the host cell, the precursor T cell is a hematopoietic stem cell. In some alternatives of the host cell, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives of the host cell, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives of the composition, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells and a host cell, wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives of the composition, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells or wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells and a host cell wherein the host cell is a precursor T cell or a hematopoietic stem cell. In some alternatives, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or

VAR2CSA. In some alternatives, the spacer comprises IgG4, IgG4-CH2 (L235D, N297Q) or IgG4-CH3. In some alternatives, the *in vitro* method for preparing a host cell of any one of the alternative host cells comprises a) providing a system of any one of the alternative systems provided herein and b) introducing the system into an isolated T lymphocyte population and expanding each T lymphocyte population in vitro. In some alternatives of the method, the T lymphocytes are expanded, and wherein the method further comprises culturing the cells in the presence of anti-CD3 and/or anti CD28, and at least one homeostatic cytokine until the cells expand sufficiently for use as a cell infusion. In some alternatives of the method, the isolated T lymphocyte population comprises precursor T cells. In some alternatives of the method, the precursor T cells are hematopoietic stem cells. In some alternatives of the method, the lymphocyte is CD8+ or CD4+. In some alternatives, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives, the spacer comprises IgG4, IgG4-CH2 (L235D, N297Q) or IgG4-CH3. In some alternatives, the polypeptide that regulates apoptosis is Survivin. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124. In some alternatives, Survivin comprises an amino acid sequence set forth in SEQ ID NO: 123.

[0017] In a seventh aspect, a method of treating, inhibiting, or ameliorating a disease in a subject in need thereof is provided. The method comprises administering to the subject the host cell of any one of the alternative host cells, such as mammalian cells, provided herein, or at least one composition or product combination of any one or more of the alternatives provided herein. The composition comprises a host cell of any one or more of alternative host cells, such as a mammalian cell, provided herein, in a pharmaceutically acceptable excipient. The host cell, such as a mammalian cell comprises a system of any one of the alternative systems described herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, the system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from a tumor specific molecule, a viral specific

molecule, or other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some

alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the side effects

are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is an inducible promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is a constitutive promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is the EF1αp. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator comprises at least one or more amino acid sequences set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12-22 or 122.. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, both vectors are packaged in a viral vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker is EGFRt and/or HER2t. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker confers drug resistance. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In

some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand, as compared to a reference chimeric receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65)

transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the systems described herein, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the systems described herein, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the systems described herein, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or a wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the systems described herein, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than

10 nM drug but not zero. In some alternatives of the systems described herein, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the systems described herein, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the systems described herein, the second nucleic acid further comprises a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized, a polynucleotide coding for a transmembrane domain, and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the systems described herein, the first promoter is in opposite orientation to the second promoter. In some alternatives of the systems described herein, the ligand binding domain is an antibody fragment, such as a binding fragment. In some alternatives of the systems described herein, the ligand binding domain is a single chain variable fragment. In some alternatives of the systems described herein, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR and/or any combinations thereof. In some alternatives of the systems described herein, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the systems described herein, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the systems described herein, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any

percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the systems described herein, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the host cell, such as a mammalian cell, the host cell is a precursor T cell. In some alternatives of the host cell, the precursor T cell is a hematopoietic stem cell. In some alternatives of the host cell, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives of the host cell, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives of the composition, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells and a host cell, wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives of the composition, the composition comprises a host cell, wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells or wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells and a host cell wherein the host cell is a precursor T cell or a hematopoietic stem cell. In some alternatives of the method, the disease is cancer or a viral disease. In some alternatives of the method, the subject is identified or selected to receive an anti-cancer therapy. In some alternatives of the method, the subject is identified or selected to receive an anti-viral therapy. In some alternatives of the method, the method further comprises measuring or evaluating an inhibition of the disease. In some alternatives of the method, the method further comprises providing said subject an additional anti-cancer therapy or anti-viral therapy before, during, or after administration of the cells of any one or more of any one of the alternatives provided herein or at least one composition or product combination of any one or more of the alternatives provided herein. In some alternatives of the method, the cells described above or

at least one composition or product combination described above are administered to said subject by adoptive cell transfer. In some alternatives of the method, the host cells described above or at least one composition or product combination described above are administered to said subject after said subject has received another form of anti-cancer therapy or anti-viral therapy. In some alternatives of the method, the method further comprises administering a drug that induces expression of a transgene in the host cell or composition for the treatment of cancer or a viral infection. In some alternatives of the method, the drug is tamoxifen and/or its metabolites, fulvestrant and/or other estrogen analogs or CMP8. In some alternatives of the method, tamoxifen is administered at a dose range of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg/dose or within a range defined by any two of the aforementioned values. In some alternatives of the method, fulvestrant is administered at a dose range of 250, 300, 350, 400, 450 or 500 mg/dose mg/dose or within a range defined by any two of the aforementioned values. In some alternatives of the method, the CMP8 is administered at a dose range to provide 30, 40 or 50 nM of drug levels in serum, or within a range defined by any two of the aforementioned values. In some alternatives of the method, the cancer is a solid tumor or hematologic malignancy. In some alternatives of the method, the solid tumor is selected from the group consisting of a breast cancer, brain cancer, lung cancer, colon cancer, renal cancer, pancreatic cancer, prostate cancer, and ovarian cancer. In some alternatives, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives, the spacer comprises IgG4, IgG4-CH2 (L235D, N297Q) or IgG4-CH3. In some alternatives, the polypeptide that regulates apoptosis is Survivin. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124. In some alternatives, Survivin comprises an amino acid sequence set forth in SEQ ID NO: 123.

[0018] In an eighth aspect, a method of treating, inhibiting, or ameliorating a disease in a subject in need thereof, is provided. The method comprises administering to the subject the host cell, such as a mammalian cell, of any one of the alternatives provided herein or at least one composition or product combination of any one or more of the alternative compositions provided herein. In some alternatives, the composition comprises a host cell of any one or more of alternative host cells, such as mammalian cells, provided herein, in a

pharmaceutically acceptable excipient. In some alternatives, the host cell, such as mammalian cells, comprises a system of any one of the alternative systems described herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, the system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from a tumor specific molecule, a viral specific molecule, or other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to

a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as

compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is an inducible promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is a constitutive promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is the EF1αp. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator comprises at least one or more amino acid sequences set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, both vectors are packaged in a viral vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second nucleic acid further

comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker is EGFRt and/or HER2t. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker confers drug resistance. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65)

transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA3 transcription factor comprises at least one or more amino acid sequences in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the systems described herein, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the systems

described herein, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the systems described herein, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or a wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the systems described herein, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the systems described herein, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the systems described herein, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the systems described herein, the second nucleic acid further comprises a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized, a polynucleotide coding for a transmembrane domain, and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the systems described herein, the first promoter is in opposite orientation to the second promoter. In some alternatives of the systems described herein, the ligand binding domain is an antibody fragment. In some alternatives of the systems described herein, the ligand binding domain is a single chain variable fragment. In some alternatives of the systems described herein, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR and/or any combinations thereof. In some alternatives of the systems described herein, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the systems

described herein, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the systems described herein, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the systems described herein, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the host cell, the host cell is a precursor T cell. In some alternatives of the host cell, such as a mammalian cell, the cell is a precursor T cell, which is a hematopoietic stem cell. In some alternatives of the host cell, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives of the host cell, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives of the composition, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells and a host cell, wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives of the composition, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells or wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells and a host cell wherein the host cell is a precursor T cell or a hematopoietic stem cell. In some alternatives of the method, the disease is cancer or a viral disease. In some alternatives of the method, the subject is identified or selected to

receive an anti-cancer therapy. In some alternatives of the method, the subject is identified or selected to receive an anti-viral therapy. In some alternatives of the method, the method further comprises measuring or evaluating an inhibition of the disease. In some alternatives of the method, the method further comprises providing said subject an additional anti-cancer therapy or anti-viral therapy before, during, or after administration of the cells of any one or more of the alternative cells described herein or at least one composition or product combination of any one or more of alternatives described herein. In some alternatives of the method, the cells of any one or more of the alternatives described herein or at least one composition or product combination of any one or more of the alternatives described herein are administered to said subject by adoptive cell transfer. In some alternatives of the method, the host cells of any one or more of the alternatives described herein or at least one composition or product combination of any one or more of the alternatives described herein are administered to said subject after said subject has received another form of anti-cancer therapy or anti-viral therapy. In some alternatives of the method, the method further comprises administering a drug that induces expression of a transgene in the host cell or composition for the treatment of cancer or a viral infection. In some alternatives of the method, the drug is tamoxifen and/or its metabolites, fulvestrant and/or other estrogen analogs or CMP8. In some alternatives of the method, tamoxifen is administered at a dose range of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg/dose or within a range defined by any two of the aforementioned values. In some alternatives of the method, the fulvestrant is administered at a dose range of 250, 300, 350, 400, 450 or 500 mg/dose mg/dose or within a range defined by any two of the aforementioned values. In some alternatives of the method, the CMP8 is administered at a dose range to provide 30, 40 or 50 nM of drug levels in serum, or within a range defined by any two of the aforementioned values. In some alternatives of the method, the cancer is a solid tumor or hematologic malignancy. In some alternatives of the method, the solid tumor is selected from the group consisting of a breast cancer, brain cancer, lung cancer, colon cancer, renal cancer, pancreatic cancer, prostate cancer, and ovarian cancer. In some alternatives, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives, the spacer comprises IgG4, IgG4-CH2 (L235D, N297Q) or IgG4-CH3. In some alternatives, the

polypeptide that regulates apoptosis is Survivin. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124. In some alternatives, Survivin comprises an amino acid sequence set forth in SEQ ID NO: 123.

[0019] In a ninth aspect, a use of the host cell, such as a mammalian cell, of any one of or more of the alternatives described herein or at least one composition or product combination of any one or more of the alternatives described herein in combination with a drug that induces expression of a transgene in the host cell or composition for the treatment of cancer or a viral infection is provided. In some alternatives, the composition comprises a host cell, such as a mammalian cell, of any one or more of alternative host cells provided herein, in a pharmaceutically acceptable excipient. In some alternatives, the host cell, such as mammalian cell, comprises a system of any one of the alternative systems described herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from a tumor specific molecule, a viral specific molecule, or any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for

inducible expression of a chimeric antigen receptor in cells, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set

forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is an inducible promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is a constitutive promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is the EF1αp. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator comprises at least one or more amino acid sequences set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system for

inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, both vectors are packaged in a viral vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker is EGFRt and/or HER2t. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker confers drug resistance. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug and wherein the system is configured to respond to an amount of the drug

that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid

sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the systems described herein, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the systems described herein, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the systems described herein, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or a wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the systems described herein, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the systems described herein, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the systems described herein, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the systems described herein, the second nucleic acid further comprises a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized, a polynucleotide coding for a transmembrane domain, and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the systems described herein, the first promoter is in opposite orientation to the second promoter.

In some alternatives of the systems described herein, the ligand binding domain is an antibody fragment. In some alternatives of the systems described herein, the ligand binding domain is a single chain variable fragment. In some alternatives of the systems described herein, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR and/or any combinations thereof. In some alternatives of the systems described herein, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the systems described herein, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the systems described herein, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the systems described herein, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the host cell, the host cell, such as a mammalian cell, is a precursor T cell. In some alternatives of the host cell, the precursor T cell is a hematopoietic stem cell. In some alternatives of the host cell, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives of the host cell, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives of the composition, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells and a host cell, wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central

memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives of the composition, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells or wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells and a host cell wherein the host cell is a precursor T cell or a hematopoietic stem cell. In some alternatives of the use, the drug is tamoxifen and/or its metabolites, fulvestrant and/or other estrogen analogs or CMP8. In some alternatives of the use, tamoxifen is administered at a dose range of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg/dose or within a range defined by any two of the aforementioned values. In some alternatives of the use, the fulvestrant is administered at a dose range of 250, 300, 350, 400, 450 or 500 mg/dose or within a range defined by any two of the aforementioned values. In some alternatives of the use, the CMP8 is administered at a dose range to provide 30, 40 or 50 nM of drug levels in serum, or within a range defined by any two of the aforementioned values. In some alternatives of the use, the cancer is a solid tumor or hematologic malignancy. In some alternatives of the use, the solid tumor is selected from the group consisting of a breast cancer, brain cancer, lung cancer, colon cancer, renal cancer, pancreatic cancer, prostate cancer, and ovarian cancer. In some alternatives, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives, the spacer comprises IgG4, IgG4-CH2 (L235D, N297Q) or IgG4-CH3. In some alternatives, the polypeptide that regulates apoptosis is Survivin. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124. In some alternatives, Survivin comprises an amino acid sequence set forth in SEQ ID NO: 123.

[0020] In a tenth aspect, a method of performing cellular immunotherapy in a subject having cancer or a viral infection is provided. The method comprises administering the host cells, such as mammalian cells, of any one or more of alternatives provided herein or at least one composition or product combination of any one or more of the alternatives provided herein to the subject and administering a drug that induces expression of a transgene in the composition or the host cells. The composition comprises a host cell of any

one or more of alternative host cells, such as mammalian cells, provided herein, in a pharmaceutically acceptable excipient. In some alternatives, the host cell, such as a mammalian cell, comprises a system of any one of the alternative systems described herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, the system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from a tumor specific molecule, a viral molecule, or other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation

domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a

concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is an inducible promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is a constitutive promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is the EF1αp. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator comprises at least one or more amino acid sequences set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, both vectors are packaged in a viral vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system for

inducible expression of a chimeric antigen receptor in cells, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker is EGFRt and/or HER2t. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker confers drug resistance. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function,

HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the systems described herein, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino

acid substitutions that allow selective binding to the drug. In some alternatives of the systems described herein, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the systems described herein, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or a wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the systems described herein, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the systems described herein, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the systems described herein, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the systems described herein, the second nucleic acid further comprises a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized, a polynucleotide coding for a transmembrane domain, and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the systems described herein, the first promoter is in opposite orientation to the second promoter. In some alternatives of the systems described herein, the ligand binding domain is an antibody fragment. In some alternatives of the systems described herein, the ligand binding domain is a single chain variable fragment. In some alternatives of the systems described herein, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR and/or any combinations thereof. In some alternatives of the systems described herein, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120

protein, or Epstein-Barr virus early antigen protein. In some alternatives of the host cell, such as a mammalian cell, the host cell is a precursor T cell. In some alternatives of the systems described herein, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the systems described herein, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the systems described herein, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the host cell, such as a mammalian cell, the cell is a precursor T cell, which is a hematopoietic stem cell. In some alternatives of the host cell, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives of the host cell, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives of the composition, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells and a host cell, wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives of the composition, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells or wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells and a host cell wherein the host cell is a precursor T cell or a hematopoietic stem cell. In some alternatives

of the method, the cancer is selected from a solid tumor or hematologic malignancy. In some alternatives of the method, the solid tumor is selected from the group consisting of a breast cancer, brain cancer, lung cancer, colon cancer, renal cancer, pancreatic cancer, prostate cancer, and ovarian cancer. In some alternatives, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives, the spacer comprises IgG4, IgG4-CH2 (L235D, N297Q) or IgG4-CH3. In some alternatives, the polypeptide that regulates apoptosis is Survivin. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124. In some alternatives, Survivin comprises an amino acid sequence set forth in SEQ ID NO: 123.

[0021] In an eleventh aspect, a use of the host cell of any one of or more of the alternatives described herein or at least one composition or product combination of any one or more of the alternatives described herein as a medicament, is provided. The composition comprises a host cell of any one or more of alternative host cells, such as mammalian cells, provided herein, in a pharmaceutically acceptable excipient. In some alternatives, the host cell, such as a mammalian cell, comprises a system of any one of the alternative systems described herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, the system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from a tumor specific molecule, a viral molecule, or other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4

chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth

in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is an inducible promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is a constitutive promoter. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second promoter is the EF1αp. In some

alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator comprises at least one or more amino acid sequences set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the transcriptional activator is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, both vectors are packaged in a viral vector. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker is EGFRt and/or HER2t. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the selectable marker confers drug resistance. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system for inducible expression of a chimeric antigen receptor in cells, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates

checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that augments transcriptional activity in response to a drug. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand.

In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the systems described herein, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the systems described herein, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the systems described herein, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or a wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the systems described herein, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the systems described herein, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 chimeric transcription factor. In some alternatives of the systems described herein, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the systems described herein, the second nucleic acid further comprises a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population,

wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized, a polynucleotide coding for a transmembrane domain, and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the systems described herein, the first promoter is in opposite orientation to the second promoter. In some alternatives of the systems described herein, the ligand binding domain is an antibody fragment. In some alternatives of the systems described herein, the ligand binding domain is a single chain variable fragment. In some alternatives of the systems described herein, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR and/or any combinations thereof. In some alternatives of the systems described herein, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the systems described herein, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the systems described herein, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the systems described herein, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the systems described herein, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the host cell, such as a mammalian cell, the host cell is a precursor T cell. In some alternatives of the host cell, the precursor T cell is a hematopoietic stem cell. In some alternatives of the host cell, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives of the host cell, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+

T cells. In some alternatives of the composition, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells and a host cell, wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives of the composition, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells or wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells and a host cell wherein the host cell is a precursor T cell or a hematopoietic stem cell. In some alternatives, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC or VAR2CSA. In some alternatives, the spacer comprises IgG4, IgG4-CH2 (L235D, N297Q) or IgG4-CH3. In some alternatives, the polypeptide that regulates apoptosis is Survivin. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124. In some alternatives, Survivin comprises an amino acid sequence set forth in SEQ ID NO: 123.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] **Figures 1A to 1F** show HEA3 (low affinity) RelA single mutant variants and HEA4 (high affinity) RelA single mutant variants and their response when dosed with 4-OHT, when they are transduced into cells. Shown in the figures is a schematic of dual-packaged lentiviral constructs housing the constitutively expressed drug-inducible transcription factors, (Fig. 1A) HEA3 or (Fig. 1B) HEA4 single mutant RelA variants (S536E or K310Q positions in the RelA protein domain, which correspond to position S846E and K621Q in HEA3 and HEA4, respectively), and a ZsGreen fluorescent reporter. ZsGreen reporter expression in Jurkat cells expressing (Fig. 1C) HEA3 or (Fig. 1D) HEA4 RelA variants following 24 hours of culture with 500 nM 4-OHT. 4-OHT dose response:

Percentage of EGFRt+ZsGreen+ cells and ZsGreen median fluorescent intensity of (Fig. 1E) HEA3 or (Fig. 1F) HEA4 RelA variant expressing Jurkat cells.

[0023] **Figures 2A to 2E** show HEA4 (high affinity) RelA double mutant variants and CMP8-responsive HEA3 RelA variants and their response when dosed with 4-OHT and CMP8, respectively, when they are transduced into cells. Shown in the figures is a schematic of dual-packaged lentiviral constructs housing the constitutively expressed drug-inducible transcription factors, (Fig. 2A) HEA4 double mutant RelA variant (S536E/K310Q positions in the RelA protein domain, which correspond to position S846E and K621Q in HEA3 and HEA4, respectively) or (Fig. 2B) CMP8-responsive HEA3 single mutant RelA variant (S563E), and a ZsGreen fluorescent reporter. ZsGreen reporter expression in Jurkat cells expressing the (Fig. 2C) HEA4 double mutant RelA variant or the (Fig. 2D) CMP8-responsive HEA3 RelA variant, following 24 hours of culture with 500 nM 4-OHT and CMP8. 4-OHT and CMP8 dose response: Percentage of EGFRt+ZsGreen+ cells and ZsGreen median fluorescent intensity of Jurkat cells expressing the (Fig. 2E) HEA4 double mutant RelA variant or (Fig. 2F) CMP8-responsive HEA3 single mutant RelA variant.

[0024] **Figures 3A to 3C** shows the results of dual-packaged lentiviral constructs encoding drug-regulated transcription factor (HEA4 (p65/S536E/K310Q)) and inducible fluorescent reporter eGFP:ffluc, when they are transduced into cells. Shown in the Fig. 3A, CD4 and CD8 T cells were transduced with dual-packaged lentiviral constructs encoding drug-regulated transcription factor (HEA4(p65/S536E/K310Q)) and inducible fluorescent reporter eGFP:ffluc. Following purification and expansion of transduced CD4 and CD8 T cells, (Fig. 3B) Western blot was performed using anti-p65 antibody to confirm expression of chimeric transcription factor. (Fig. 3C) EGFRt expression was confirmed in sorted cells by flow cytometry, and leakiness of eGFP expression in the absence of inducing ligand was determined.

[0025] **Figures 4A to 4B** shows the dual-packaged lentiviral constructs encoding drug-regulated transcription factor (HEA4(p65/S536E/K310Q)) and inducible fluorescent reporter eGFP:ffluc and the results when the lentiviral constructs are transduced into cells. (Fig. 4A) CD4 and CD8 T cells were transduced with dual-packaged lentiviral constructs encoding drug-regulated transcription factor (HEA4(p65/S536E/K310Q)) and inducible fluorescent reporter eGFP:ffluc. Following purification and expansion of transduced CD4

and CD8 T cells, (Fig. 4B) T cells were incubated with 0 nM, 30 nM, or 500 nM of 4-OHT in the presence or absence of aCD3/aCD28 microbeads (2:1 bead:cell ratio) or PMA (2 uM)/Ionomycin (20 ng/mL) for 24 hours. eGFP expression was subsequently quantified by flow cytometry.

[0026] **Figures 5A to 5E** shows dual-packaged lentiviral constructs encoding drug-regulated transcription factor (HEA4(p65/S536E/K310Q)) and inducible fluorescent reporter eGFP:ffluc and the results when the lentiviral constructs are transduced into cells. (Fig. 5A) CD4 and CD8 T cells were transduced with dual-packaged lentiviral constructs encoding drug-regulated transcription factor (HEA4(p65/S536E/K310Q)) and inducible fluorescent reporter eGFP:ffluc. Following purification and expansion of transduced CD4 and CD8 T cells, T cells were incubated with increasing concentrations of 4-OHT in the presence or absence of aCD3/aCD28 microbeads (2:1 bead:cell ratio) or PMA (2 uM)/Ionomycin (20 ng/mL) for 24 hours. eGFP expression was quantified by flow cytometry. (Fig. 5B) %EGFRt+eGFP+ CD4 and (Fig. 5C) CD8 T cells and (Fig. 5D) MFI of eGFP expression in (Fig. 5D) CD4 and (Fig. 5E) CD8 T cells following 24 hours of treatment with 4-OHT.

[0027] **Figures 6A to 6D** shows results of cells transduced with lentiviral constructs. Jurkat cells were transduced with dual-packaged lentiviral constructs encoding drug-regulated transcription factor (HEA4(p65/S536E/K310Q)) and inducible (Fig. 6A) chimeric cytokine receptor (CCR(CD122)) or (Fig. 6B) Survivin linked to Her2tG via a cleavable 2A linker. Expression of (Fig. 6C) CCR(CD122) and (Fig. 6D) Survivin following 24 hours of treatment with 500 nM 4-OHT was determined by Her2tG upregulation.

Detailed Description

[0028] In the description that follows, the terms should be given their plain and ordinary meaning when read in light of the specification. One of skill in the art would understand the terms as used in view of the whole specification.

[0029] "About" has its plain and ordinary meaning when read in light of the specification, and may be used, for example, when referring to a measurable value and may be meant to encompass variations of ±20% or ±10%, more preferably ±5%, even more preferably ±l%, and still more preferably ±0.1 % from the specified value.

[0030] “Antigen" or "Ag," have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a molecule that provokes an immune response. This immune response can involve either antibody production, or the activation of specific immunologically-competent cells, or both. It is readily apparent that an antigen can be generated synthesized, produced recombinantly or can be derived from a biological sample. Such a biological sample can include, but is not limited to a tissue sample, a tumor sample, a cell or a biological fluid such, for example, blood, plasma or ascites fluid. In some alternatives of the systems provided herein, the ligand recognized by a chimeric antigen receptor is an antigen, capable of provoking an immune response.

[0031] "Anti-tumor effect" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a biological effect, which can be manifested by a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in the number of metastases, an increase in life expectancy, or a decrease of various physiological symptoms associated with the cancerous condition. An "anti-tumor effect" can also be manifested by a decrease in recurrence or an increase in the time before recurrence.

[0032] “Chimeric receptor” has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a synthetically designed receptor comprising a ligand binding domain of an antibody or other protein sequence that binds to a molecule associated with the disease or disorder and is linked via a spacer domain to one or more intracellular signaling domains of a T cell or other receptors, such as a costimulatory domain. Chimeric receptor can also be referred to as artificial T cell receptors, chimeric T cell receptors, chimeric immunoreceptors, and chimeric antigen receptors (CARs). These CARs are engineered receptors that can graft an arbitrary specificity onto an immune receptor cell. The term chimeric antigen receptors or “CARs” are also considered by some investigators to include the antibody or antibody fragment, the spacer, signaling domain, and transmembrane region. Due to the surprising effects of modifying the different components or domains of the CAR described herein, such as the epitope binding region (for example, antibody fragment, scFv, or portion thereof), spacer, transmembrane domain, and/ or signaling domain), the components of the CAR are

frequently distinguished throughout this disclosure in terms of independent elements. The variation of the different elements of the CAR can, for example, lead to stronger binding affinity for a specific epitope or antigen.

[0033] A "single-chain variable fragment (scFv)" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a fusion protein that can have variable regions of the heavy (VH) and light chains (VL) of immunoglobulins, connected with a short linker peptide of ten to 25 amino acids. The linker is usually rich in glycine for flexibility, as well as serine or threonine for solubility, and can either connect the N-terminus of the VH with the C-terminus of the VL, or vice versa. This protein retains the specificity of the original immunoglobulin, despite removal of the constant regions and the introduction of the linker. The scFv can be specific for an antigen. "Antigen" or "Ag" as used herein refers to a molecule that provokes an immune response. This immune response can involve either antibody production, or the activation of specific immunologically-competent cells, or both. An antigen can be generated, synthesized, produced recombinantly or can be derived from a biological sample. Such a biological sample can include, but is not limited to a tissue sample, a tumor sample, a cell or a biological fluid such, for example, blood, plasma or ascites fluid. In some alternatives of the CARs provided herein, the CAR comprises an antibody fragment, scFv, or portion thereof e.g., a polypeptide comprising the CDR domains. In some alternatives, the scFv specifically binds to CD19. This particular scFv is referred to as huCD19 scFv (G01S) and is encoded by SEQ ID NO: 40 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagaggtgcagctggtcgaatccgg aggaggactggtccagcccggccggagcctgagactgagctgtgccgcttccggattcacttttgacgattacgcaatgcattgggtg aggcaggcccctggcaaggggctggaatgggtctccggaatctcttggaacagtgggcgcattggatatgccgattctgtgaaggg ccgattcactatctctcgggacaacgctaaaaatagtctgtttctgcagatgaattccctgcgcgccgaggataccgccgtgtactattg cgcccgagaccagggctaccactactatgatagcgccgaacatgcattcgacatttggggacagggaactgtggtcaccgtgagctc cggaggaggaggaagcggaggaggagggtccggaggcgggggatcacagagcgcactgacccagccacggagcgtgagcg gatttcctgggcagtctgtcaccattagttgcacaggcaccacatcagacgatgtgagctggtaccagcagcacccagggaaggctc cccagctgatgctgtatgacgtgtccaaaagaccttctggcgtcccacataggtttagtggaagccggagcggccgggcagccagtc tgatcatttcagggctgcagacagaggacgaagctgattatttctgttctagttacgcaggcagatataactctgtgctgtttggcgggg gaacaaagctgactgtcctg). In some alternatives, the CAR comprises an scFv. In some

alternatives, the scFv comprises an huCD19 scFv (G01S) amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 41 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMH WVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDT AVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQ PRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSR SGRAASLIISGLQTEDEADYFCSSYAGRYNSVLFGGGTKLTVL). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 41.

[0034] In some alternatives, the scFv is encoded by the muCD19 (FMC63) scFv nucleotide sequence. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 42 (Atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccgacatccagatgacccagac cacctccagcctgagcgccagcctgggcgaccgggtgaccatcagctgccgggccagccaggacatcagcaagtacctgaactg gtatcagcagaagcccgacggcaccgtcaagctgctgatctaccacaccagccggctgcacagcggcgtgcccagccggtttagc ggcagcggctccggcaccgactacagcctgaccatctccaacctggaacaggaagatatcgccacctacttttgccagcagggcaa cacactgccctacacctttggcggcggaacaaagctggaaatcaccggcagcacctccggcagcggcaagcctggcagcggcga gggcagcaccaagggcgaggtgaagctgcaggaaagcggccctggcctggtggcccccagccagagcctgagcgtgacctgca ccgtgagcggcgtgagcctgcccgactacggcgtgagctggatccggcagccccccaggaagggcctggaatggctgggcgtga tctggggcagcgagaccacctactacaacagcgccctgaagagccggctgaccatcatcaaggacaacagcaagagccaggtgtt cctgaagatgaacagcctgcagaccgacgacaccgccatctactactgcgccaagcactactactacggcggcagctacgccatgg actactggggccagggcaccagcgtgaccgtgagcagc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 43 (MLLLVTSLLLCELPHPAFLLIPDIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWY QQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLP YTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVSGVS LPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSL QTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 43.

[0035] In some alternatives, the scFv is encoded by a CD20 (CD20 (Leu16)) nucleic acid sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 44 (atggagacagacacactcctgctatgggtgctgctgctctgggttccaggttccacaggtgacattgtgctgacccaatctccagctat cctgtctgcatctccaggggagaaggtcacaatgacttgcagggccagctcaagtgtaaattacatggactggtaccagaagaagcc aggatcctccccaaaccctggatttatgccacatccaacctggcttctggagtccctgctcgcttcagtggcagtgggtctgggacct cttactctctcacaatcagcagagtggaggctgaagatgctgccacttattactgccagcagtggagttttaatccacccacgttcggag gggggaccaagctggaaataaaaggcagtactagcggtggtggctccgggggcggttccggtgggggcggcagcagcgaggtg cagctgcagcagtctggggctgagctggtgaagcctggggcctcagtgaagatgtcctgcaaggcttctggctacacatttaccagtt acaatatgcactgggtaaagcagacacctggacagggcctggaatggattggagctatttatccaggaaatggtgatacttcctacaat cagaagttcaaaggcaaggccacattgactgcagacaaatcctccagcacagcctacatgcagctcagcagcctgacatctgagga ctctgcggactattactgtgcaagatctaattattacggtagtagctactggttcttcgatgtctggggcgcagggaccacggtcaccgt ctcctca). In some alternatives, the CD20 (Leu 16) scFv comprises an amino acid sequence set forth in SEQ ID NO: 45 (METDTLLLWVLLLWVPGSTGDIVLTQSPAILSASPGEKVTMTCRASSSVNYMDWY QKKPGSSPKPWIYATSNLASGVPARFSGSGSGTSYSLTISRVEAEDAATYYCQQWSF NPPTFGGGTKLEIKGSTSGGGSGGGSGGGGSSEVQLQQSGAELVKPGASVKMSCKAS GYTFTSYNMHWVKQTPGQGLEWIGAIYPGNGDTSYNQKFKGKATLTADKSSSTAY MQLSSLTSEDSADYYCARSNYYGSSYWFFDVWGAGTTVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 45.

[0036] In some alternatives, the scFv is encoded by a CD22 (m971) scFv nucleotide sequence. In some alternatives, the scFv specifically binds to CD22. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 46 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtacagctgcagcagtcagg tccaggactggtgaagccctcgcagaccctctcactcacctgtgccatctccggggacagtgtctctagcaacagtgctgcttggaac tggatcaggcagtccccatcgagaggccttgagtggctgggaaggacatactacaggtccaagtggtataatgattatgcagtatctgt gaaaagtcgaataaccatcaacccagacacatccaagaaccagttctccctgcagctgaactctgtgactcccgaggacacggctgt gtattactgtgcaagagaagtgactggggatctcgaggatgcttttgatatctggggccaagggacaatggtcaccgtctcctcaggc ggaggggctctggcggcggaggatctgggggaggggcagcgacatccagatgacccagtctccatcgtccctgtctgcatctgt aggagacagagtcaccatcacttgccgggcaagccagaccatttggagctacttaaattggtatcagcagagaccagggaaagccc

ctaacctcctgatctatgctgcatccagtttgcaaagtggggtcccatcaaggttcagtggcaggggatctgggacagatttcactctca ccatcagcagtctgcaagctgaagattttgcaacttactactgtcaacagagttacagtatccctcagacttttggccaggggaccaagc tggagatcaaacgaact). In some alternatives, the scFv comprises a CD22 (m971) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 47 (MLLLVTSLLLCELPHPAFLLIPQVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAW NWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPED TAVYYCAREVTGDLEDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSDIQMTQSPSS LSASVGDRVTITCRASQTIWSYLNWYQQRPGKAPNLLIYAASSLQSGVPSRFSGRGS GTDFTLTISSLQAEDFATYYCQQSYSIPQTFGQGTKLEIKRT). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 47.

[0037] In some alternatives, the scFv comprises a B7H3 (hBRCA84D) scFv nucleotide sequence. In some alternatives, the scFv binds specifically to the B7-H3 receptor. The B7-H3 receptor is known to be expressed on a variety of cancer cells. Without being limiting, these cancer cells can included gastric, ovarian and/or non-small cell lung cancers. In some alternatives, the CAR is used in the treatment or amelioration of cancer and/or inflammation. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 48 (atgctgcgtcggcggggcagccctggcatgggtgtgcatgtgggtgcagccctgggagcactgtggttctgcctcacaggagccc tggaggtccaggtccctgaagacccagtggtggcactggtgggcaccgatgccaccctgtgctgctccttctcccctgagcctggctt cagcctggcacagctcaacctcatctggcagctgacagataccaaacagctggtgcacagctttgctgagggccaggaccagggca gcgcctatgccaaccgcacggccctcttcccggacctgctggcacagggcaacgcatccctgaggctgcagcgcgtgcgtgtggc ggacgagggcagcttcacctgcttcgtgagcatccgggatttcggcagcgctgccgtcagcctgcaggtggccgctccctactcgaa gcccagcatgaccctggagcccaacaaggacctgcggccaggggacacggtgaccatcacgtgctccagctaccagggctaccct gaggctgaggtgttctggcaggatgggcagggtgtgcccctgactggcaacgtgaccacgtcgcagatggccaacgagcagggct tgtttgatgtgcacagcatcctgcgggtggtgctgggtgcaaatggcacctacagctgcctggtgcgcaaccccgtgctgcagcagg atgcgcacagctctgtcaccatcacagggcagcctatgacattcccccagaggccctgtgggtgaccgtggggctgtctgtctgtct cattgcactgctggtggccctggctttcgtgtgctggagaaagatcaaacagagctgtgaggaggagaatgcaggagctgaggacc aggatggggagggagaaggctccaagacagccctgcagcctctgaaacactctgacagcaaagaagatgatggacaagaaatag cc). In some alternatives, the scFv comprises a B7H3 (hBRCA84D) scFv amino acid

sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 49 (MLRRRGSPGMGVHVGAALGALWFCLTGALEVQVPEDPVVALVGTDATLCCSFSPE PGFSLAQLNLIWQLTDTKQLVHSFAEGQDQGSAYANRTALFPDLLAQGNASLRLQR VRVADEGSFTCFVSIRDFGSAAVSLQVAAPYSKPSMTLEPNKDLRPGDTVTITCSSYQ GYPEAEVFWQDGQGVPLTGNVTTSQMANEQGLFDVHSILRVVLGANGTYSCLVRN PVLQQDAHSSVTITGQPMTFPPEALWVTVGLSVCLIALLVALAFVCWRKIKQSCEEE NAGAEDQDGEGEGSKTALQPLKHSDSKEDDGQEIA). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 49.

[0038] In some alternatives, the scFv comprises the L1CAM (CE7) scFv nucleotide sequence. In some alternatives, the scFv is specific for the epitope, CE7 epitope, of L1CAM. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 50 (atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggtgcagctgcagcagcct ggcgccgagctggtgaagccaggcgccagcgtgaagctgtcctgcaaggccagcggctacaccttcaccggctactggatgcact gggtgaagcagagacccggccacggcctggaatggatcggcgagatcaaccccagcaacggccggaccaactacaacgagcgg ttcaagagcaaggccaccctgaccgtggacaagagcagcaccaccgccttcatgcagctgtccggcctgaccagcgaggacagcg ccgtgtacttctgcgccagggactactacggcaccagctacaacttcgactactggggccagggcaccacactgaccgtgagcagc ggcggaggggctctggcggcggaggatctgggggaggggcagcgacatccagatgacccagagcagcagcagcttcagcg tgagcctgggcgaccgggtgaccatcacctgtaaggccaacgaggacatcaacaaccggctggcctggtatcagcagacccccgg caacagccccaggctgctgatcagcggcgccaccaacctggtgaccggcgtgcccagccggtttagcggcagcggctccggcaa ggactacaccctgaccatcacaagcctgcaggccgaggacttcgccacctactactgccagcagtactggtccacccccttcaccttc ggcagcggcaccgagctggaaatcaaa). In some alternatives, the scFv comprises the L1CAM (CE7) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 51 (MLLLVTSLLLCELPHPAFLLIPQVQLQQPGAELVKPGASVKLSCKASGYTFTGYWM HWVKQRPGHGLEWIGEINPSNGRTNYNERFKSKATLTVDKSSTTAFMQLSGLTSEDS AVYFCARDYYGTSYNFDYWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSSSSFS VSLGDRVTITCKANEDINNRLAWYQQTPGNSPRLLISGATNLVTGVPSRFSGSGSGK DYTLTITSLQAEDFATYYCQQYWSTPFTFGSGTELEIK). In some alternatives, the scFv

is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 51.

[0039] In some alternatives, the scFv is encoded by the EGFR (cetuximab) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 52 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtgcagctgaaacagagcg gcccgggcctggtgcagccgagccagagcctgagcattacctgcaccgtgagcggctttagcctgaccaactatggcgtgcattgg gtgcgccagagcccgggcaaaggcctggaatggctgggcgtgatttggagcggcggcaacaccgattataacaccccgtttacca gccgcctgagcattaacaaagataacagcaaaagccaggtgtttttttaaaatgaacagcctgcagagcaacgataccgcgatttattat tgcgcgcgcgcgctgacctattatgattatgaatttgcgtattggggccagggcaccctggtgaccgtgagcgcgggcggcggcgg cagcggcggcggcggcagcggcggcggcggcagcgatattctgctgacccagagcccggtgattctgagcgtgagcccgggcg aacgcgtgagctttagctgccgcgcgagccagagcattggcaccaacattcattggtatcagcagcgcaccaacggcagcccgcgc ctgctgattaaatatgcgagcgaaagcattagcggcattccgagccgctttagcggcagcggcagcggcaccgattttaccctgagc attaacagcgtggaaagcgaagatattgcggattattattgccagcagaacaacaactggccgaccacctttggcgcgggcaccaaa ctggaactgaaacgcacc). In some alternatives, the scFv comprises the EGFR scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 53 (MLLLVTSLLLCELPHPAFLLIPQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHW VRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIY YCARALTYYDYEFAYWGQGTLVTVSAGGGGSGGGGSGGGGSDILLTQSPVILSVSP GERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSI NSVESEDIADYYCQQNNNWPTTFGAGTKLELKRT). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 53.

[0040] In some alternatives, the scFv comprises the EGFRVIII (806) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 54 (atgctgctgctggtgacaagcctgctgctgtgcgagctgccacaccctgctttcctgctgatccctgatgtgcagctgcaggaatcag gcccaagcctggtcaaaccctcccagtctctgagtctgacctgtacagtgactgggtactccatcacatctgatttcgcatggaactgg attaggcagtttccaggcaataagctggagtggatgggctacatctcatatagcgggaacactcgctataatcccagtctgaaatcacg gatcagcattactagagacaccagcaagaaccagttctttctgcagctgaattccgtgaccattgaggataccgccacatactattgcgt

cacagctggcagaggctttccatactggggacagggcacactggtgactgtcagcgccggctccacctctgggagtggaaaacctg gctccggggaaggatctacaaagggagacatcctgatgactcagtccccaagctccatgtcagtgagcctgggcgacaccgtctcta ttacatgtcactctagtcaggatatcaacagtaatattggctggctgcagcagcgacccggcaagtctttcaaagggctgatctatcatg gaactaacctggacgatgaagtgcctagcagattttccggctctgggagtggagctgattacagtctgaccatttcaagcctggagtca gaagacttcgcagattactattgcgtccagtatgcccagttcccctggacttttggcgggggaaccaagctggagatcaaacgg). In some alternatives, the scFv comprises the EGFRVIII (806) scFv amino acid sequence. In some alternatives, the scFv comprises the amino acid sequence set forth in SEQ ID NO: 55 (MLLLVTSLLLCELPHPAFLLIPDVQLQESGPSLVKPSQSLSLTCTVTGYSITSDFAWN WIRQFPGNKLEWMGYISYSGNTRYNPSLKSRISITRDTSKNQFFLQLNSVTIEDTATY YCVTAGRGFPYWGQGTLVTVSAGSTSGSGKPGSGEGSTKGDILMTQSPSSMSVSLG DTVSITCHSSQDINSNIGWLQQRPGKSFKGLIYHGTNLDDEVPSRFSGSGSGADYSLTI SSLESEDFADYYCVQYAQFPWTFGGGTKLEIKR). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 55.

[0041] In some alternatives, the scFv is encoded by the EphA2 (2A4) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 56 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtgcagctgttggagtctggg ggaggcttggtacagcctgggggtccctgagactctcctgtgcagcctctggattcacctttagcagctataccatgtcttgggtgcg acaggcccctggacaagcgcttgagtggatgggaaccattagtagtcgtggtacttacacctactatccagacagtgtgaagggccg attcaccatctccagagacaacgccaagaactcactgtatctgcaaatgaacagcctgagagccgaggacacggctgtgtattactgt gcgagagaagctatctttactcactggggccgtggcaccctggtcaccgtctcctcaggtggtggtggttctggcggcggcggctcc ggtggtggtggttctgacatccagttgacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcacttgcaaggc gagtcaggacattaataactatcacagctggtaccagcagaaacctggccaggctcccaggctcctcatctatcgtgcaaacagattg gtcgatggggtcccagacaggttcagtggcagcgggtatggaacagattttaccctcacaattaataacatagaatctgaggatgctg catattacttctgtctgaaatataatgtgtttccgtacacgttcggccaagggaccaaggtggagatcaaa). In some alternatives, the scFv comprises the EphA2 (2A4) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 57 (MLLLVTSLLLCELPHPAFLLIPQVQLLESGGGLVQPGGSLRLSCAASGFTFSSYTMS WVRQAPGQALEWMGTISSRGTYTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCAREAIFTHWGRGTLVTVSSGGGGSGGGGSGGGGSDIQLTQSPSSLSASVGDR

VTITCKASQDINNYHSWYQQKPGQAPRLLIYRANRLVDGVPDRFSGSGYGTDFTLTI NNIESEDAAYYFCLKYNVFPYTFGQGTKVEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 57.

[0042] In some alternatives, the scFv is encoded by the EpHA2 (4H5) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 58 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtgcagctgttggagtctggg ggaggcttggtacagcctgggggggtccctgagactctcctgtgcagcctctggattcacctttagcagctataccatgtcttgggtgcg acaggcccctggacaagcgcttgagtggatgggaaccattagtagtggtggtacttacacctactatccagacagtgtgaagggccg attcaccatctccagagacaacgccaagaactcactgtatctgcaaatgaacagcctgagagccgaggacacggctgtgtattactgt gcgagagaagctatctttacttactggggccgtggcaccctggtcaccgtctcctcaggtggtggtggttctggcggcggcggctccg gtggtggtggttctgacatccagttgacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcacttgcaaggcg agtcaggacattaataactatttaagctggtaccagcagaaacctggccaggctcccaggctcctcatctatcgtgcaaacagattggt agatggggtcccagacaggttcagtggcagcgggtatggaacagattttaccctcacaattaataacatagaatctgaggatgctgcat attacttctgtctgaaatatgatgtgtttccgtacacgttcggccaagggaccaaggtggagatcaaa). In some alternatives, the scFv comprises the EpHA2 (4H5) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 59 (MLLLVTSLLLCELPHPAFLLIPQVQLLESGGGLVQPGGSLRLSCAASGFTFSSYTMS WVRQAPGQALEWMGTISSGGTYTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCAREAIFTYWGRGTLVTVSSGGGGSGGGGSGGGGSDIQLTQSPSSLSASVGDR VTITCKASQDINNYLSWYQQKPGQAPRLLIYRANRLVDGVPDRFSGSGYGTDFTLTI NNIESEDAAYYFCLKYDVFPYTFGQGTKVEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 59.

[0043] In some alternatives, the scFv is encoded by a FITC (E2) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 60 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaagcgtgctgacacagcctagctc cgtgtctgccgcccctggccagaaagtgaccatcagctgtagcggcagcaccagcaacatcggcaacaactacgtgtcctggtatca gcagcaccccggcaaggcccccaagctgatgatctacgacgtgtccaagcggcccagcggcgtgcccgatagattttccggcagc

aagagcggcaacagcgccagcctggatatcagcggcctgcagtctgaggacgaggccgactactattgcgccgcctgggacgata gcctgagcgagttcctgtttggcaccggcaccaagctgacagtgctgggcggaggcggaggatctggcggcggaggaagtggcg gaggggatctcaggtgcagctggtggaaagcggcggcaacctggtgcagcctggcggatctctgagactgagctgtgccgccag cggcttcaccttcggcagcttcagcatgagctgggtgcgccaggctcctgggggaggactggaatgggtggcaggactgagcgcc agaagcagcctgacccactacgccgatagcgtgaagggccggttcaccatcagccgggacaacgccaagaacagcgtgtacctgc agatgaacagcctgcgggtggaagataccgccgtgtactactgcgccagacggtcctacgacagcagcggctactggggccacttc tacagctacatggacgtgtggggccagggcaccctcgtgacagtgtct). In some alternatives, the scFv comprises the FITC (E2) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequences set forth in SEQ ID NO: 61 (MLLLVTSLLLCELPHPAFLLIPSVLTQPSSVSAAPGQKVTISCSGSTSNIGNNYVSWY QQHPGKAPKLMIYDVSKRPSGVPDRFSGSKSGNSASLDISGLQSEDEADYYCAAWD DSLSEFLFGTGTKLTVLGGGGGSGGGGSGGGGSQVQLVESGGNLVQPGGSLRLSCA ASGFTFGSFSMSWVRQAPGGGLEWVAGLSARSSLTHYADSVKGRFTISRDNAKNSV YLQMNSLRVEDTAVYYCARRSYDSSGYWGHFYSYMDVWGQGTLVTVS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 61.

[0044] In some alternatives, the scFv is encoded by the GD2 (hu3F8) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 62 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaagcatcgtgatgacccagacccc caagttcctgctggtgagcgccggcgacagggtgaccatcacctgcaaggccagccagagcgtgagcaacgacgtgacctggtac cagcagaaggccggccagagccccaagctgctgatctacagcgccagcaacaggtacagcggcgtgcccgacaggttcaccggc agcggctacggcaccgccttcaccttcaccatcagcaccgtgcaggccgaggacctggccgtgtacttctgccagcaggactacag cagcttcggcggcggcaccaagctggagatcaagagg). In some alternatives, the scFv comprises the GD2 (hu3F8) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 63 (MLLLVTSLLLCELPHPAFLLIPSIVMTQTPKFLLVSAGDRVTITCKASQSVSNDVTWY QQKAGQSPKLLIYSASNRYSGVPDRFTGSGYGTAFTFTISTVQAEDLAVYFCQQDYS SFGGGTKLEIKR). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 63.

[0045] In some alternatives, the scFv is encoded by the Her2 (Herceptin) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 64 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatatccagatgacccagtccccg agctccctgtccgcctctgtgggcgatagggtcaccatcacctgccgtgccagtcaggatgtgaatactgctgtagcctggtatcaaca gaaaccaggaaaagctccgaaactactgatttactcggcatccttcctctactctggagtcccttctcgcttctctggttccagatctggg acggatttcactctgaccatcagcagtctgcagccggaagacttcgcaacttattactgtcagcaacattatactactcctcccacgttcg gacagggtaccaaggtggagatcaaaggcagtactagcggcggtggctccgggggcggatccggtgggggcggcagcagcga ggttcagctggtggagtctggcggtggcctggtgcagccaggggctcactccgtttgtcctgtgcagcttctggcttcaacattaaag acacctatatacactgggtgcgtcaggccccgggtaagggcctggaatgggttgcaaggatttatcctacgaatggttatactagatat gccgatagcgtcaagggccgtttcactataagcgcagacacatccaaaaacacagcctacctgcagatgaacagcctgcgtgctga ggacactgccgtctattattgttctagatggggaggggacggcttctatgctatggactactggggtcaaggaaccctggtcaccgtct cgagt). In some alternatives, the scFv comprises the Her2 (Herceptin) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 65 (MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAW YQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTT PPTFGQGTKVEIKGSTSGGGSGGGSGGGGSSEVQLVESGGGLVQPGGSLRLSCAASG FNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 65.

[0046] In some alternatives, the scFv is encoded by the IL13R2a (hu08) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 66 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagacatccagatgacccagtcccc ctcttctctgtctgcctctgtgggcgacagagtgaccatcacctgtaaggccagtcaggatgtaggtactgctgtagcctggtatcagca gaagcctggcaaggctcccaagctgctgatctactcggcatcctaccggtccactggcgtgccttccagattctccggctctggctctg gcaccgatttcaccctgaccatctcctccctccagcctgaggatttcgccacctactactgccagcaccattatagtgctccgtggacgt ttggcggcggaacaaaggtggagatcaagggtggtggtggttctggcggcggcggctccggtggtggtggttctgaggtgcagctg gtggagtctggcggcggactggtgcagcctggcggctctctgagactgtcttgtgccgcctccggcttcaccttcagtaggaatggca

tgtcttgggtgaggcaggcccctggcaagggcctggagtgggtggccaccgttagtagtggtggtagttacatctactatgcagaca gtgtgaaggggcggttcaccatctccagggacaacgccaagaactccctgtacctccagatgaactccctgagggccgaggatacc gccgtgtactactgtgc). In some alternatives, the scFv comprises the IL13Ra2 (hu08) VlVh scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 67 (MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCKASQDVGTAVAW YQQKPGKAPKLLIYSASYRSTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQHHYS APWTFGGGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGF TFSRNGMSWVRQAPGKGLEWVATVSSGGSYIYYADSVKGRFTISRDNAKNSLYLQ MNSLRAEDTAVYYC). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 67.

[0047] In some alternatives, the scFv is encoded by an IL13Ra2 (hu08) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 68 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagaggtgcagctggtggagtctgg cggcggactggtgcagcctggcggctctctgagactgtcttgtgccgcctccggcttcaccttcagtaggaatggcatgtcttgggtga ggcaggcccctggcaagggcctggagtgggtggccaccgttagtagtggtggtagttacatctactatgcagacagtgtgaagggg cggttcaccatctccagggacaacgccaagaactccctgtacctccagatgaactccctgagggccgaggataccgccgtgtactac tgtgccagacaagggactacggcactagctacgaggttcttcgatgtctggggccagggcaccctggtgaccgtgtcctctggtggt ggtggttctggcggcggcggctccggtggtggtggttctgacatccagatgacccagtccccctcttctctgtctgcctctgtgggcga cagagtgaccatcacctgtaaggccagtcaggatgtaggtactgctgtagcctggtatcagcagaagcctggcaaggctcccaagct gctgatctactcggcatcctaccggtccactggcgtgccttccagattctccggctctggctctggcaccgatttcaccctgaccatctc ctccctccagcctgaggatttcgccacctactactgccagcaccattatagtgctccgtggacgtttggcggcggaacaaaggtggag atcaaggaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 hu08 VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 69 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFSRNGMS WVRQAPGKGLEWVATVSSGGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARQGTTALATRFFDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSS LSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIYSASYRSTGVPSRFSGSGS

GTDFTLTISSLQPEDFATYYCQHHYSAPWTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 69.

[0048] In some alternatives, the scFv is encoded by an IL13Ra2 (hu07) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 70 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatattcagatgacccagagccc gagcagcctgagcgcgagcgtgggcgatcgcgtgaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggt atcagcagaaaccgggcaaagcgccgaaactgctgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcgg cagcggcagcggcaccgattttaccctgaccattagcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgca gcccgctgacctttggcggcggcaccaaagtggaaattaaaggtggtggtggttctggcggcggcggctccggtggtggtggttctg aagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacct ttaccaaatatggcgtgcattgggtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagca ccgattataacagcgcgctgatgagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgc gcgcggaagataccgcggtgtattattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtg agcagcgaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 71 (MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCTASLSVSSTYLHWY QQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCHQYHRSP LTFGGGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFT KYGVHWVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARDHRDAMDYWGQGTLVTVSSESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 71.

[0049] In some alternatives, the scFv is encoded by the IL13Ra2 (hu07) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 72 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagaagtgcagctggtggaaagcg gcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacctttaccaaatatggcgtgcattgg gtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagcaccgattataacagcgcgctgat

gagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgcgcgcggaagataccgcggtgt attattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtgagcagcggtggtggtggttctg gcggcggcggctccggtggtggtggttctgatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatcgcgt gaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggtatcagcagaaaccgggcaaagcgccgaaactgc tgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcggcagcggcagcggcaccgattttaccctgaccatta gcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgcagcccgctgacctttggcggcggcaccaaagtgga aattaaagaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 73 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFTKYGVH WVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNSLRAED TAVYYCARDHRDAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCTASLSVSSTYLHWYQQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCHQYHRSPLTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 73.

[0050] In some alternatives, the antibody or portion thereof or scFv is encoded by the Anti-IL13Ra2 (IL13 zetakine) nucleotide sequence. In some alternatives, the antibody or portion thereof or scFv is encoded by a sequence set forth in SEQ ID NO: 74 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaggccctgtgcctccctctacagcc ctcaggtacctcattgaggagctggtcaacatcacccagaaccagaaggctccgctctgcaatggcagcatggtatggagcatcaac ctgacagctggcatgtactgtgcagccctggaatccctgatcaacgtgtcaggctgcagtgccatcgagaagacccagaggatgctg agcggattctgcccgcacaaggtctcagctgggcagttttccagcttgcatgtccgagacaccaaaatcgaggtggcccagtttgtaa aggacctgctcttacatttaaagaaacttttcgcgagggacggttcaa). In some alternatives, the antibody or portion thereof or scFv comprises an Anti-IL13Ra2 (IL13 zetakine) amino acid sequence. In some alternatives, the antibody or portion thereof or scFv comprises an amino acid sequence set forth in SEQ ID NO: 75 (MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSI NLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQ FVKDLLLHLKKLFREGRF). In some alternatives, the scFv is encoded by a nucleic acid

sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 75.

[0051] In some alternatives, the scFv is encoded by an oaGD2 (8B6) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 76 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatgttgtgatgacccaaactcca ctctccctgcctgtcagtcttggagatcaagcctcaatctcttgcagatctagtcagagccttctaaaaaataatggaaacacctttttaca ttggtacctgcagaagtcaggccagtctccaaagctccttatctacaaagtttccaaccgactttctggggtcccagacaggttcagtgg cagtggatcagggacatatttcacactcaagatcagcagagtggaggctgaggatctgggagtttatttctgctctcaaagtacacatat tccgtacacattcggaggggggaccaagctcgagctgaaacgaggcggaggggctctggcggcggaggatctgggggagggg gcagcgaggtgaaactggtggagtctggaggaggcttggtgctgcctggggattctctgagactctcctgtgcaacttctgagttcac cttcactgattactacatgacttgggtccgccagcctccaagaaaggcacttgagtggttgggttttattagaaacagagctaatggttac acaacagagtacaatccatctgtgaagggtcggttcaccatttccagagataattcccaaagcatcctctatcttcaaatgaacaccctg agaactgaggacagtgccacttattactgtgcaagagtctctaactgggcctttgactactggggccaaggcaccactctcacagtctc ctca). In some alternatives, the scFv comprises the oaGD2 (8B6) VlVh scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 77 (MLLLVTSLLLCELPHPAFLLIPDVVMTQTPLSLPVSLGDQASISCRSSQSLLKNNGNT FLHWYLQKSGQSPKLLIYKVSNRLSGVPDRFSGSGSGTYFTLKISRVEAEDLGVYFCS QSTHIPYTFGGGTKLELKRGGGGSGGGGSGGGGSEVKLVESGGGLVLPGDSLRLSCA TSEFTFTDYYMTWVRQPPRKALEWLGFIRNRANGYTTEYNPSVKGRFTISRDNSQSIL YLQMNTLRTEDSATYYCARVSNWAFDYWGQGTTLTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 77.

[0052] In some alternatives, the scFv is encoded by an ROR1 (R12) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 78 (atgctgctgctggtgacaagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggaacagctcgtcgaaagc ggcggcagactggtgacacctggcggcagcctgaccctgagctgcaaggccagcggcttcgacttcagcgcctactacatgagctg ggtccgccaggcccctggcaagggactggaatggatcgccaccatctaccccagcagcggcaagacctactacgccacctgggtg aacggacggttcaccatctccagcgacaacgcccagaacaccgtggacctgcagatgaacagcctgacagccgccgaccgggcc

acctacttttgcgccagagacagctacgccgacgacggcgccctgttcaacatctggggccctggcaccctggtgacaatctctagc ggcggaggcggatctggtggcggaggaagtggcggcggaggatctgagctggtgctgacccagagcccctctgtgtctgctgccc tgggaagccctgccaagatcacctgtaccctgagcagcgcccacaagaccgacaccatcgactggtatcagcagctgcagggcga ggcccccagatacctgatgcaggtgcagagcgacggcagctacaccaagaggccaggcgtgcccgaccggttcagcggatctag ctctggcgccgaccgctacctgatcatccccagcgtgcaggccgatgacgaggccgattactactgtggcgccgactacatcggcg gctacgtgttcggcggaggcacccagctgaccgtgaccggc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 79 (ROR1 (R12) scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQEQLVESGGRLVTPGGSLTLSCKASGFDFSAYYMSW VRQAPGKGLEWIATIYPSSGKTYYATWVNGRFTISSDNAQNTVDLQMNSLTAADRA TYFCARDSYADDGALFNIWGPGTLVTISSGGGGSGGGGSGGGGSELVLTQSPSVSAA LGSPAKITCTLSSAHKTDTIDWYQQLQGEAPRYLMQVQSDGSYTKRPGVPDRFSGSS SGADRYLIIPSVQADDEADYYCGADYIGGYVFGGGTQLTVTG). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 79.

[0053] In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 80 (CD33 (h2H12) VhVl scFv nucleotide sequence (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggttcagctggtgcagtctgga gctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggttacacctttaccaattatgatataaattgggtgag acaggcccctggacaagggcttgagtggattggatggatttatcctggagatggtagtaccaaatataatgagaaattcaaggccaag gctaccctgacagctgacacatccaccagcacagcctacatggagctgaggagcctgagatctgatgacacagctgtgtattactgtg cttctggatatgaagatgctatggactactgggggcaagggaccacagtcacagtctcctca). In some alternatives, the scFv is specific for CD33. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 81 (CD33 (h2H12) VhVl scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYDIN WVRQAPGQGLEWIGWIYPGDGSTKYNEKFKAKATLTADTSTSTAYMELRSLRSDDT AVYYCASGYEDAMDYWGQGTTVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 81.

[0054] In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 82 (CD33 (h2H12) VlVh scFv nucleotide sequence: atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagacatccagatgacccagtctccat

cctcactgtctgcatctgtaggagacagagtcaccatcaattgtaaggctagtcaggacattaatagctatttgagctggtttcagcaga aaccagggaaagcccctaagaccctgatctatagagcaaatagattggtagatggggtcccatcaaggttctctggcagtggatctgg gcaagattatactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgcttgcagtatgatgagtttcctctcacatttgg aggagggaccaaggtggagatcaaa). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 83 (CD33 (h2H12) VlVh scFv amino acid sequence: MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTINCKASQDINSYLSWFQ QKPGKAPKTLIYRANRLVDGVPSRFSGSGSGQDYTLTISSLQPEDFATYYCLQYDEFP LTFGGGTKVEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 83.

[0055] In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 84 (Mesothelin (P4) scFv nucleotide sequence: atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtacagctgcagcagtcaggt ccaggactcgtgacgccctcgcagaccctctcactcacctgtgccatctccggggacagtgtctctagcaacagtgctacttggaact ggatcaggcagtccccatcgagaggccttgagtggctgggaaggacatactacaggtccaagtggtataacgactatgcagtatctg tgaaaagtcgaatgagcatcaacccagacacatccaagaaccagttctccctgcagctgaactctgtgactcccgaggacacggctg tgtattactgtgcaagaggaatgatgacttactattacggtatggacgtctggggccaagggaccacggtcaccgtctcctcaggaatt ctaggatcc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 85 (Mesothelin (P4) scFv amino acid sequence: MLLLVTSLLLCELPHPAFLLIPQVQLQQSGPGLVTPSQTLSLTCAISGDSVSSNSATWN WIRQSPSRGLEWLGRTYYRSKWYNDYAVSVKSRMSINPDTSKNQFSLQLNSVTPED TAVYYCARGMMTYYYGMDVWGQGTTVTVSSGILGS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 85.

[0056] In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 86 (VAR2CSA (ID1-DBL2Xb) scFv nucleotide sequence: atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaagtctcacgaatgggtataagtgcg acaaatgcaaatcaggcacatcccggtccaaaaaaaaatggatctggaaaaagagcagcgggaatgaggagggcctgcaggaag aatacgctaacacaatcggactgccccctcgaactcaatctctgtaccttgggaacttgcctaaactggaaaacgtctgtgaagacgtc aaggacataaacttcgatacgaaagagaagttcctggctggatgccttatcgtgagctttcacgagggaaagaatctgaagaaaaggt acccacagaataaaaactctggcaataaagagaatttgtgcaaggccctggagtactcttttgcggactatggcgatctcataaagggc acaagcatctgggataatgagtataccaaggatctggagctgaatctgcagaataactttgggaaattgtttgggaagtatattaaaaaa

aataataccgccgagcaggacacatcctactcttccctcgacgagctgcgggagtcatggtggaacaccaacaaaaagtatatctgg acggcaatgaaacatggcgcggaaatgaatatcaccacttgtaatgcagacggctctgtcaccgggtccggttcttcttgcgatgatat accaaccatcgatttgattccgcagtatctgagatttctccaagagtgggtggaaaatttttgcgagcagaggcaagctaaggtcaagg acgtgatcaccaattgtaaaagttgcaaagaatcagggaacaagtgcaaaaccgagtgtaagacgaagtgcaaggacgaatgcgag aaatataaaaaattcatcgaggcttgtggaacagccgggggtgggattgggaccgcaggcagcccatggagcaagcggtgggacc aaatctataaacgatacagcaagcacatcgaagatgccaagcggaaccgcaaagctggcacaaaaaactgtgggactagcagcac gactaatgccgcggcaagcactgatgaaaataaatgcgtgcaaagtgacatcgactctttcttcaaacacctgatcgatatcggtcttac tacgccaagcagctacctcagtaatgttctggatgataatatttgtggggcggacaaagcaccttggactacctacaccacctatacca caacagagaagtgtaataaagagagagacaaatcaaagtctcagagctctgatacactggtcgttgtgaatgtgccaagccctttggg gaatacgccctacagatataaatac). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 87 (VAR2CSA (ID1-DBL2Xb) scFv amino acid sequence: MLLLVTSLLLCELPHPAFLLIPSLTNGYKCDKCKSGTSRSKKKWIWKKSSGNEEGLQ EEYANTIGLPPRTQSLYLGNLPKLENVCEDVKDINFDTKEKFLAGCLIVSFHEGKNLK KRYPQNKNSGNKENLCKALEYSFADYGDLIKGTSIWDNEYTKDLELNLQNNFGKLF GKYIKKNNTAEQDTSYSSLDELRESWWNTNKKYIWTAMKHGAEMNITTCNADGSV TGSGSSCDDIPTIDLIPQYLRFLQEWVENFCEQRQAKVKDVITNCKSCKESGNKCKTE CKTKCKDECEKYKKFIEACGTAGGGIGTAGSPWSKRWDQIYKRYSKHIEDAKRNRK AGTKNCGTSSTTNAAASTDENKCVQSDIDSFFKHLIDIGLTTPSSYLSNVLDDNICGA DKAPWTTYTTYTTTEKCNKERDKSKSQSSDTLVVVNVPSPLGNTPYRYKY). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 87.

[0057] "Spacer", can also be referred to as a "linker," and has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, residues which resides between the light and the heavy chains. The spacer can be 10 to 20 amino acids in length (*e.g.*, at least, equal to 10, 11, 12, 13, 14, 15, 16, 17, 19, or 20 amino acids or a length within a range defined by any two of the aforementioned lengths). The flexible spacer allows the scFv domain to orient in multiple directions in order to enable an optimized antigen binding specificity. The scFv domain can be preceded by a signal peptide so as to direct the nascent protein to the endoplasmic reticulum and subsequent surface expression, whereby cleavage can occur. A flexible spacer can also allow the scFv domain to orient in different directions to facilitate antigen binding. A good spacer for

allowing specific binding of the scFv domain can be determined empirically and is dependent on the scFv domain antigen recognition domain. In some alternatives, the linker comprises optimized spacer lengths so as to improve binding of scFv domain to the target cell, which may increase cytotoxic efficacy. In some alternatives, the linker or spacer between the scFv domain and the transmembrane can be 25 to 55 amino acids in length (*e.g.*, at least, equal to 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, or 55 amino acids or a length within a range defined by any two of the aforementioned lengths. In some alternatives, the spacer is encoded by the nucleic acid sequence set forth in SEQ ID NO: 102 (IgG4 hinge nucleotide sequence: gagagcaagtacggaccgccctgccccccttgccct). In some alternatives, the spacer comprises an amino acid sequence set forth in SEQ ID NO: 103 (IgG4 hinge amino acid sequence: ESKYGPPCPPCP). In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 103. In some alternatives, the spacer is encoded by a nucleic acid sequence set forth in SEQ ID NO: 104 (IgG4-CH2(L235D, N297Q) nucleotide sequence; gcccccgagttcgacggcggacccagcgtgttcctgttcccccccaagcccaaggacaccctgatgatcagccggacccccgaggtgacctgcgtggtggtggacgtgagccaggaagatcccgaggtccagttcaattggtacgtggacggcgtggaagtgcacaacgccaagaccaagcccagagaggaacagttccagagcacctaccgggtggtgtctgtgctgaccgtgctgcaccaggactggctgaacggcaaagaatacaagtgcaaggtgtccaacaagggcctgcccagcagcatcgaaaagaccatcagcaaggccaag). In some alternatives, the spacer comprises an amino acid sequence set forth in SEQ ID NO: 105 (IgG4-CH2(L235D, N297Q) amino acid sequence; APEFDGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHN AKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK). In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 105. In some alternatives, the spacer is encoded by a nucleic acid sequence set forth in SEQ ID NO: 106 (IgG4-CH3 nucleotide sequence: ggccagcctcgcgagccccaggtgtacaccctgcctccctcccaggaagagatgaccaagaaccaggtgtccctgacctgcctggtgaagggcttctaccccagcgacatcgccgtggagtgggagagcaacggccagcctgagaacaactacaagaccacccctcccgtgctggacagcgacggcagcttcttcctgtacagccggctgaccgtggacaagagccggtggcaggaaggcaacgtctttagctgcagcgtgatgcacgaggccctgcacaaccactacacccagaagagcctgagcctgtccctgggcaag). In some alternatives,

the spacer comprises an amino acid sequence set forth in SEQ ID NO: 107 (IgG4 CH3 amino acid sequence: GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK). In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 107. In some alternatives, the spacer is encoded by a nucleic acid sequence set forth in SEQ ID NO: 108 (CD8 hinge/Transmembrane domain nucleotide sequence: gaatctaagtacggaccggccaagcctaccaccaccctgcccctagacctccaacacccgccccaacaatcgccagccagcctct gtctctgaggcccgaggcttgtagaccagctgctggcggagccgtgcacaccagaggactggatttcgcctgcgacatctacatctg ggcccctctggccggcacatgtggcgtgctgctgagcctcgtgatcacc). In some alternatives, the spacer comprises an amino acid sequence set forth in SEQ ID NO: 109 (CD8 hinge/Transmembrane domain amino acid sequence: ESKYGPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIW APLAGTCGVLLLSLVIT. In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 109.

[0058] "Transmembrane domain" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a transmembrane region of a protein. This may be a single alpha helix, a transmembrane beta barrel, a beta-helix, or any other structure. In some alternatives herein, the transmembrane domain comprises CD28tm. In some alternatives, the transmembrane domain is encoded by a sequence set forth in SEQ ID NO: 110 (CD28 transmembrane domain nucleotide sequence: atgttctgggtgctggtggtggtcggaggcgtgctggcctgctacagcctgctggtcaccgtggccttcatcatcttttgggtg). In some alternatives, the transmembrane domain comprises an amino acid sequence set forth in SEQ ID NO: 111 (CD28 transmembrane domain amino acid sequence: MFWVLVVVGGVLACYSLLVTVAFIIFWV). In some alternatives, the transmembrane domain is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 111. In some alternatives, the transmembrane domain is encoded by a sequence set forth in SEQ ID NO: 112 (CD8 hinge/Transmembrane domain nucleotide sequence:

gaatctaagtacggaccggccaagcctaccaccacccctgcccctagacctccaacacccgccccaacaatcgccagccagcctct gtctctgaggcccgaggcttgtagaccagctgctggcggagccgtgcacaccagaggactggatttcgcctgcgacatctacatctg ggcccctctggccggcacatgtggcgtgctgctgctgagcctcgtgatcacc). In some alternatives, the transmembrane domain comprises an amino acid sequence set forth in SEQ ID NO: 113 (CD8 hinge/Transmembrane domain amino acid sequence: ESKYGPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIW APLAGTCGVLLLSLVIT). In some alternatives, the transmembrane domain is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 113.

[0059] A “chimeric cytokine receptor,” has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a protein that has an amino acid sequence of a chemokine or portion thereof and is a fusion protein with another protein.

[0060] “Intracellular signaling domain,” or "Co-stimulatory domain," has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a signaling moiety that provides to T cells a signal which, in addition to the primary signal provided by for instance the CD3 zeta chain of the TCR/CD3 complex, mediates a T cell response, including, but not limited to, activation, proliferation, differentiation, cytokine secretion, and the like. A co-stimulatory domain can include all or a portion of, but is not limited to, CD27, CD28, 4-1BB, OX40, CD30, CD40, ICOS, lymphocyte function-associated antigen-l (LFA-l), CD2, CD7, LIGHT, NKG2C, B7-H3, or a ligand that specifically binds with CD83. In some alternatives, the co-stimulatory domain is an intracellular signaling domain that interacts with other intracellular mediators to mediate a cell response including activation, proliferation, differentiation and cytokine secretion, and the like. In some alternatives of the signaling domain described herein, the signaling domain comprises CD3ζ, CD28 cytoplasmic domain, and/or 4-1BB. In some alternatives, the intracellular signaling domain is encoded by a nucleic acid sequence set forth in SEQ ID NO: 114 (CD3 Zeta nucleotide sequence: cgggtgaagttcagcagaagcgccgacgcccctgcctaccagcagggccagaatcagctgtacaacgagctgaacctgggcaga agggaagagtacgacgtcctggataagcggagaggccgggaccctgagatgggcggcaagcctcggcggaagaacccccagg aaggcctgtataacgaactgcagaaagacaagatggccgaggcctacagcgagatcggcatgaagggcgagcggaggcggggc

aagggccacgacggcctgtatcagggcctgtccaccgccaccaaggatacctacgacgccctgcacatgcaggccctgcccccaa gg). In some alternatives, the intracellular signaling domain comprises an amino acid sequence set forth in SEQ ID NO: 115 (CD3 Zeta amino acid sequence: RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQ EGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQAL PPR). In some alternatives, the intracellular signaling domain is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 115. In some alternatives, the intracellular signaling domain is encoded by a nucleic acid sequence set forth in SEQ ID NO: 116 (4-1BB nucleotide sequence: aaacggggcagaaagaaactcctgtatatattcaaacaaccatttatgagaccagtacaaactactcaagaggaagatggctgtagct gccgatttccagaagaagaagaaggaggatgtgaactg). In some alternatives, the intracellular signaling domain comprises an amino acid sequence set forth in SEQ ID NO: 117 (4-1BB amino acid sequence: KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL). In some alternatives, the intracellular signaling domain is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 117. In some alternatives, the intracellular signaling domain is encoded by a sequence set forth in SEQ ID NO: 118 (CD28 cytoplasmic domain nucleotide sequence: cgcagcaagcggagcagaggcggccacagcgactacatgaacatgacccctagacggcctggccccaccagaaagcactacca gccctacgccctccccgggactttgccgcctacagaagc). In some alternatives, the intracellular signaling domain comprises an amino acid sequence set forth in SEQ ID NO: 119 (CD28 cytoplasmic domain amino acid sequence: RSKRSRGGHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS). In some alternatives, the intracellular signaling domain is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 119.

[0061] As used herein, “nucleic acid” or “nucleic acid molecule” has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), oligonucleotides, fragments generated by the polymerase chain reaction (PCR), and fragments generated by any of ligation, scission, endonuclease action, and exonuclease action. Nucleic acid molecules can be composed of monomers that are naturally-occurring nucleotides (such as DNA and RNA), or analogs of naturally-occurring nucleotides (e.g., enantiomeric forms of

naturally-occurring nucleotides), or a combination of both. Modified nucleotides can have alterations in sugar moieties and/or in pyrimidine or purine base moieties. Sugar modifications include, for example, replacement of one or more hydroxyl groups with halogens, alkyl groups, amines, and azido groups, or sugars can be functionalized as ethers or esters. Moreover, the entire sugar moiety can be replaced with sterically and electronically similar structures, such as aza-sugars and carbocyclic sugar analogs. Examples of modifications in a base moiety include alkylated purines and pyrimidines, acylated purines or pyrimidines, or other well-known heterocyclic substitutes. Nucleic acid monomers can be linked by phosphodiester bonds or analogs of such linkages. Analogs of phosphodiester linkages include phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoranilidate, phosphoramidate, and the like. The term "nucleic acid molecule" also includes so-called "peptide nucleic acids," which comprise naturally-occurring or modified nucleic acid bases attached to a polyamide backbone. Nucleic acids can be either single stranded or double stranded.

[0062] "DNA spacer" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a spacer comprising nucleotides. A DNA spacer may reside in between a promoter and a gene that is to be expressed that is under control of the promoter, for example. In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values.

"Coding for" and "encoding" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other macromolecules such as a defined sequence of amino acids. Thus, a gene codes for a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. A

"nucleic acid sequence coding for a polypeptide" includes all nucleotide sequences that are degenerate versions of each other and that code for the same amino acid sequence.

[0063] "Survivin," is also known as baculoviral inhibitor of apoptosis repeat-containing 5 or BIRC5, and has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, a protein that is a member of the inhibitor of apoptosis family. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK ETNNKKKEFEETVKKVRRAIEQLAAMD).

[0064] "Conditional" or "Inducible" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, nucleic acid construct that includes a promoter that provides for gene expression in the presence of an inducer and does not substantially provide for gene expression in the absence of the inducer.

[0065] "Constitutive" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, the nucleic acid construct that includes a promoter that is constitutive providing for expression of a polypeptide that is continuously produced.

[0066] "Specific" or "Specificity" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, the characteristic of a ligand for the binding partner or alternatively, the binding partner for the ligand, and can include complementary shape, charge and hydrophobic specificity for binding. Specificity for binding can include stereospecificity, regioselectivity and chemoselectivity. In some alternatives, a method of making a nucleic acid encoding a

chimeric antigen receptor is provided such that a nucleic acid encoding a chimeric antigen receptor is generated, wherein the chimeric antigen receptor binds specifically to a desired or selected ligand.

[0067] "TamR-tf" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, tamoxifen regulated transcription factors. Without being limiting, tamoxifen regulated transcription factors can include wild-type HEA3, wild-type HEA4, mutant HEA3, mutant HEA4 and/or RelA variants.

[0068] "HEA3" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a chimeric transcription factor composed of human subunits including the N-terminal DNA binding domain of Hepatocyte Nuclear Factor 1-alpha (HNF-1α) fused in frame to the mutant tamoxifen-specific ligand binding domain of the estrogen receptor ligand binding domain (ER-LBD) which contains 1 amino acid substitution (G521R), which ablates binding of estradiol but confers nanomolar estrogen analogues, that is in turn fused to the p65 activation domain of NF-κB (p65).

[0069] HEA-3 has been described by Roscilli *et al.* (Molecular Therapy, Vol. 6, Issue 5, pp. 653-663 (2002)) as a novel 4-hydroxytamoxifen (4-OHT) dependent regulator which was shown to have long term control of gene expression in mouse skeletal muscle (Roscilli *et al.*; included by reference in its entirety herein.)

[0070] "HEA4" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a chimeric transcription factor composed of human subunits including the N-terminal DNA binding domain of Hepatocyte Nuclear Factor 1-alpha (HNF-1α) fused in frame to the tamoxifen-specific ligand binding domain of the estrogen receptor ligand binding domain (ER-LBD) which contains 3 amino acid substitutions (G400V, M543A, L544A) that ablate binding of estradiol but confers nanomolar sensitivity to estrogen analogues, that is in turn fused to the p65 activation domain of NF-κB (p65).

[0071] "Regulate" or "modulate" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, the act of

controlling a biological process, or to exert a modifying or controlling influence on a biological or cellular process or pathway.

[0072] "Cytotoxic T lymphocyte "(CTL) has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a T lymphocyte that expresses CD8 on the surface thereof (e.g., a $CD8^+$ T cell). In some alternatives, such cells are preferably "memory" T cells (T_M cells) that are antigen-experienced. In some alternatives, the host cells comprising the alternative systems provided herein are CTL cells.

[0073] "Central memory" T cell (or "T_{CM}") has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, an antigen experienced CTL that expresses CD62L, CCR-7 and/or CD45RO on the surface thereof, and does not express or has decreased expression of CD45RA, as compared to naive cells. In some alternatives, central memory cells are positive for expression of CD62L, CCR7, CD28, CD127, CD45RO, and/or CD95, and may have decreased expression of CD54RA, as compared to naïve cells. "Effector memory" T cell (or "T_{EM}") as used herein refers to an antigen experienced T cell that does not express or has decreased expression of CD62L on the surface thereof, as compared to central memory cells, and does not express or has a decreased expression of CD45RA, as compared to naïve cell. In some alternatives, effector memory cells are negative for expression of CD62L and/or CCR7, as compared to naïve cells or central memory cells, and may have variable expression of CD28 and/or CD45RA. In some alternatives, the host cells comprising the alternative systems provided herein are T_{CM} cells. In some alternatives of the host cells provided herein, the host cell is a central memory T cell.

[0074] "Naïve " T cells has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a non-antigen experienced T lymphocyte that expresses CD62L and/or CD45RA, and does not express CD45RO-, as compared to central or effector memory cells. In some alternatives, naïve CD8+ T lymphocytes are characterized by the expression of phenotypic markers of naïve T cells including CD62L, CCR7, CD28, CD127, and/or CD45RA. In some alternatives, the host cells comprising the alternative systems provided herein are naïve T cells.

[0075] “Effector “ “T_E” T cells has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, antigen experienced cytotoxic T lymphocyte cells that do not express or have decreased expression of CD62L, CCR7, and/or CD28, and are positive for granzyme B and/or perforin, as compared to central memory or naïve T cells. In some alternatives, the host cells comprising the alternative systems provided herein are effector T cells.

[0076] "Enriched" and "depleted" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, amounts of cell types in a mixture and subjecting of the mixture of the cells to a process or step, which results in an increase in the number of the "enriched" type and a decrease in the number of the "depleted" cells. Thus, depending upon the source of the original population of cells subjected to the enriching process, a mixture or composition may contain 60, 70, 80, 90, 95, or 99 percent or more (in number or count) of the "enriched" cells and/or 40, 30, 20, 10, 5 or 1 percent or less (in number or count) of the "depleted" cells. In some alternatives, an *in vitro* method for preparing a host cell of any one of any one of the alternatives is provided herein. The *in vitro* method comprises a) providing a system of any one of the alternatives described herein, and b) introducing the system into an isolated T lymphocyte population and expanding each T lymphocyte population in vitro. The process of expanding each T lymphocyte population is a process of enriching the T lymphocyte population.

[0077] “Epitope” has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a part of an antigen or molecule that is recognized by the immune system including antibodies, T cells, and/or B cells. Epitopes usually have at least 7 amino acids and can be linear or conformational. In some alternatives herein, an antibody or ligand binding domain can be optimized to bind a specific epitope. Techniques for optimizing binding can be appreciated by those skilled in the art. For example, a ligand binding motif can be optimized by point mutation in order to increase binding affinity and/or epitope recognition.

[0078] "Isolated," has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, various polypeptides or nucleic acids that have been identified and separated and/or recovered from a component of its natural environment. Preferably, the isolated polypeptide or nucleic acid is free of

association with all components with which it is naturally associated. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide or nucleic acid, and can include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. Isolated can also be used to describe isolation of a subpopulation of cells, such as, for example isolation of subpopulations of CD4+ and/or CD8+ T lymphocytes during methods of manufacturing cells for use.

[0079] "Intracellular signaling domain" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, all or a portion of one or more domains of a molecule (here the chimeric receptor molecule) that provides for activation of a lymphocyte. Intracellular domains of such molecules mediate a signal by interacting with cellular mediators to result in proliferation, differentiation, activation and other effector functions. In some alternatives, such molecules include all or portions of CD28, CD3, or 4-1BB, or combinations thereof.

[0080] "Ligand" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a substance that binds specifically to another substance to form a complex. Examples of ligands include epitopes on antigens, molecules that bind to receptors, substrates, inhibitors, hormones, and/or activators. "Ligand binding domain" as used herein refers to substance or portion of a substance that binds to a ligand. Examples of ligand binding domains include antigen binding portions of antibodies, extracellular domains of receptors, and/or active sites of enzymes. "Operably linked" as used herein refers to functional linkage between a regulatory sequence and a heterologous nucleic acid sequence resulting in expression of the latter. For example, a first nucleic acid sequence is operably linked with a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Generally, operably linked DNA sequences are contiguous and, where necessary to join two proteins coding regions, in the same reading frame.

[0081] "Tumor specific molecule," has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, tumor-typical

antigens, proteins or molecules expressed by a tumor. In some of the alternatives described herein, the tumor specific molecule is CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, or MAGE A3 TCR or combinations thereof.

[0082] A "viral molecule" or "viral specific molecule" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a protein encoded by a viral RNA or DNA, or a molecule that is expressed by a cell in reaction to a viral infection. In some alternatives described herein the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein.

[0083] "Percent (%) amino acid sequence identity" with respect to the chimeric receptor polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference sequence for each of the ligand binding domain, spacer, transmembrane domain, and/or the lymphocyte activating domain, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared. For example, % amino acid sequence identity values generated using the WU-BLAST-2 computer program [Altschul et al., Methods in Enzymology, 266:460-480 (1996); herein incorporated by reference] uses several search parameters, most of which are set to the default values. Those that are not set to default values (i.e., the adjustable parameters) are set with the following values: overlap span=1, overlap fraction=0.125, word threshold (T) =11 and scoring matrix=BLOSUM62. A % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acid residues between each or all of the polypeptide amino acid sequence of the reference chimeric receptor sequence and the

comparison amino acid sequence of interest as determined by WU-BLAST-2 by (b) the total number of amino acid residues of the polypeptide of interest. In some alternatives, the percent sequence identity of amino acids or nucleic acids are determined by computer software.

[0084] "Substantially purified" refers to a molecule that has 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% or less other molecule types or other cell types. A substantially purified cell also refers to a cell, which has been separated from other cell types with which it is normally associated in its naturally occurring state. In some instances, a population of substantially purified cells refers to a homogenous population of cells.

[0085] "Not substantially found" when used in reference the presence of a tumor antigen or other molecules on normal cells refers to the percentage of a normal cell type that has the antigen or molecule, and/or the density of the antigen on the cells. In some alternatives, not substantially found means that the antigen or molecule is found on less than 50% of normal cell type and/or at a 50% less density as compared to the amount of cells or antigen found on a tumor cell or other diseased cell.

[0086] "T cells" or "T lymphocytes" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, can be T-cells from any mammal, preferably a primate, species, including monkeys, dogs, and/or humans. In some alternatives of the host cells provided herein, the host cells are T cells, wherein the T cells are allogeneic (from the same species but different donor) as the recipient subject; in some alternatives the T cells are autologous (the donor and the recipient are the same); in some alternatives the T cells are syngeneic (the donor and the recipients are different but are identical twins).

[0087] "Vector" or "construct" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, nucleic acid used to introduce heterologous nucleic acids into a cell that has regulatory elements to provide expression of the heterologous nucleic acids in the cell. Vectors include but are not limited to plasmid, minicircles, yeast, transposons, and viral genomes. In some alternatives, the vectors are plasmid, minicircles, yeast, transposons, or viral genomes. In some alternatives, the transposons are piggy bac transposons. In some alternatives of the systems

provided herein, the first and/or second nucleic acid reside on a vector. In some alternatives, the vector is a viral vector.

[0088] "Transgene" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a gene or genetic material that has been transferred naturally, or by any of a number of genetic engineering techniques from one organism to another. In some alternatives described herein, a method is provided for inducible expression of a transgene in cells, the system comprising: a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes the transgene; and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity. In some alternatives, the transgene encodes a protein that modulates T cells.

[0089] A viral vector can be used to deliver genetic material into a cell. Delivery of the vector can be performed by transduction and the technique is known to those skilled in the art. In some alternatives herein, a vector for introducing the nucleic acid into a cell is an adenovirus viral vector or a lentivirus viral vector.

[0090] "Minicircles," have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, small circular plasmid derivatives that have been freed or liberated from prokaryotic vector components. Minicircles can serve as an expression vector, where they have been applied as transgene carriers for the genetic modification of mammalian cells, with the advantage that, since they contain no bacterial DNA sequences, they are less likely to be perceived as foreign and

destroyed. As such, typical transgene delivery methods involve plasmids, which contain foreign DNA. The smaller size of minicircles also extends their cloning capacity and facilitates their delivery into cells. Without being limiting, the preparation of minicircles can follow a two-step procedure, which can involve production of a parental plasmid (bacterial plasmid with eukaryotic inserts) in *E. coli* and induction of a site-specific recombinase at the end of this process but still in bacteria. These steps can be followed by the excision of prokaryotic vector parts via two recombinase-target sequences at both ends of the insert and recovery of the resulting minicircle (vehicle for the highly efficient modification of the recipient cell) and the miniplasmid by capillary gel electrophoresis (CGE).

[0091] The purified minicircle can be transferred into the recipient cell by transfection, by electroporation, or by other methods known to those skilled in the art. Conventional minicircles can lack an origin of replication, so they cannot replicate within the target cells and the encoded genes will disappear as the cell divides (which can be either an advantage or disadvantage depending on whether the application demands persistent or transient expression). Some alternatives utilize a gene delivery polynucleotide for stable insertion of a nucleic acid into a gene, wherein the nucleic acid for insertion is flanked by inverted terminal repeat gene sequences in the gene delivery polynucleotide, and wherein the gene delivery polynucleotide is selectable. In some alternatives, the gene delivery polynucleotide is a minicircle.

[0092] Plasmids containing transposon systems such as *Sleeping Beauty* (SB) or *piggyBac* offer a non-viral approach for stably introducing genes into T-cells. Recently, the *piggyBac* system was used to produce stably-transfected mammalian cells expressing multiple transgenes of interest by delivery of multiple transposons. The SB system, first reactivated for mammalian cell use by Ivics and coworkers, has been used as the gene delivery modality in clinical trials of T-cell immunotherapy. Gene integration by SB has weaker preference for transcriptional units and their regulatory sequences compared to the γ-retroviral and lentiviral vectors and is therefore considered to be safer. In some alternatives described herein, genetic modification by minicircles comprising the Sleeping Beauty system are contemplated. In some alternatives described herein, genetic modification by minicircles comprising the *piggyBac* system are contemplated. In some alternatives described herein,

genetic modification by minicircles comprising the Sleeping Beauty system are contemplated.

[0093] "Apoptosis" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, the process of programmed cell death (PCD) that can occur in multicellular organisms. Biochemical events lead to characteristic cell changes (morphology) and death. These changes include blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. In apoptosis, a cell initiates intracellular apoptotic signaling in response to stress, which can bring about cell suicide. The binding of nuclear receptors by glucocorticoids, heat, radiation, nutrient deprivation, viral infection, hypoxia and increased intracellular calcium concentration, for example, by damage to the membrane, can all trigger the release of intracellular apoptotic signals by a damaged cell. A number of cellular components, such as poly ADP ribose polymerase, can also help regulate apoptosis.

[0094] Before the actual process of cell death is precipitated by enzymes, apoptotic signals must cause regulatory proteins to initiate the apoptosis pathway. This step allows apoptotic signals to cause cell death, or the process to be stopped, should the cell no longer need to die. Several proteins are involved, but two main methods of regulation have been identified: targeting mitochondria functionality, or directly transducing the signal via adaptor proteins to the apoptotic mechanisms. Another extrinsic pathway for initiation identified in several toxin studies is an increase in calcium concentration within a cell caused by drug activity, which also can cause apoptosis via a calcium binding protease calpain.

[0095] Apoptosis can be regulated by many factors. These factors can include but are not limited to genes that can express IL-2, IL-7, IL-15, Chemokine receptors, Bcl2, CA-Akt, dn-TGFbetaRIII, dn-SHP1/2, and/or PD-1CD28 chimeras. IL-15 regulates T and natural killer cell activation and proliferation. In rodent lymphocytes, IL-15 was shown to prevent apoptosis by inducing an apoptosis inhibitor, BCL2L1/BCL-X(L). In humans with celiac disease, IL-15 similarly suppresses apoptosis in T-lymphocytes by inducing Bcl-2 and/or BCL-xL. Bcl-2 (B-cell lymphoma 2), encoded in humans by the BCL2 gene, is the founding member of the Bcl-2 family of regulator proteins that regulate cell death (apoptosis), by either inducing (pro-apoptotic) it or inhibiting it (anti-apoptotic). Bcl-2 is specifically considered as an important anti-apoptotic protein and is, thus classified as an oncogene.

Protein kinase B (PKB), also known as Akt, is a serine/threonine-specific protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription and cell migration. In some alternatives, a system for inducible expression of a gene that regulates a T cell function is provided, wherein the system comprises: a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives, the polypeptide that regulates apoptosis or modulates checkpoint signaling comprises IL-2, IL-7, IL-15, chemokine receptors, Bcl2, CA-Akt, dn-TGFbetaRIII, dn-SHP1/2 or PD-1CD28 chimeras.

[0096] "Checkpoint signaling" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, blocking the cell cycle at specific transition points, and/or checkpoints to ensure that the events of the cell cycle take place in the correct order. Checkpoint signaling can also be activated. By way of example and not of limitation, checkpoint signaling can occur by damage to the DNA so that the cell cycle does not have to proceed until the damage is repaired. "Cell cycle checkpoints" are control mechanisms in eukaryotic cells which ensure proper division of the cell. Each checkpoint serves as a potential halting point along the cell cycle, during which the conditions of the cell are assessed, with progression through the various phases of the cell cycle occurring when favorable conditions are met. Currently, there are three known checkpoints: the G1 checkpoint, also known as the restriction or start checkpoint; the G2/M checkpoint; and the metaphase checkpoint, also known as the spindle checkpoint. The

biochemical pathways that restrain cell cycle transition and/or induce cell death after stress are known as cell cycle checkpoints. These checkpoints maintain the fidelity of DNA replication, repair, and division. Polypeptides that can regulate checkpoint signaling can include but are not limited to p53, p107, p130, and transcriptional repressor Rb. In some alternatives of the systems provided herein, the polypeptide that modulates checkpoint signaling comprises p53, p107, p130 or transcriptional repressor Rb.

[0097] "Negative checkpoint regulators" have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, factors that can restrict the ability of T-cell responses to effectively attack tumors. They are also referred to as negative checkpoint signaling. In some alternatives, a system for inducible expression of a transgene is provided. In some alternatives, the transgene encodes a chimeric antigen receptor. In some alternatives, a system for inducible expression of chimeric antigen receptor in cells is provided. In some alternatives of the systems for inducible expression of a gene that regulates a T cell function, the polypeptide that modulates checkpoint signaling is a negative checkpoint regulator comprising PD-1, VISTA, LAG-3 or TIM3. In some alternatives, the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3.

[0098] In another example, cell cycle inhibitors mediating the growth inhibitory cues of upstream signaling pathways, the cyclin-CDK inhibitors of the Cip/Kip family p21Cip1, p27Kip1, and p57Kip2 have emerged as multifaceted proteins with functions beyond cell cycle regulation. In addition to regulating the cell cycle, Cip/Kip proteins can also play important roles in apoptosis, transcriptional regulation, cell fate determination, cell migration and cytoskeletal dynamics. A complex phosphorylation network modulates Cip/Kip protein functions by altering their subcellular localization, protein-protein interactions, and stability. These functions are essential for the maintenance of normal cell and tissue homeostasis, in processes ranging from embryonic development to tumor suppression. In some alternatives, a system for inducible expression of a transgene is provided. In some alternatives, the transgene encodes a chimeric antigen receptor. In some alternatives, a system for inducible expression of a transgene is provided. In some

alternatives, the transgene encodes a chimeric antigen receptor. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, is provided. In some alternatives of the system for inducible expression of a gene that regulates a T cell function, the polypeptide modulates checkpoint signaling. In some alternatives, the polypeptide that modulates checkpoint signaling inhibits negative checkpoint regulators. In some alternatives, the negative checkpoint regulator comprises PD-1, VISTA, LAG-3 and/or TIM3.

[0099] "T cell precursors" have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, lymphoid precursor cells that can migrate to the thymus and become T cell precursors, which do not express a T cell receptor. All T cells originate from hematopoietic stem cells in the bone marrow. Hematopoietic progenitors (lymphoid progenitor cells) from hematopoietic stem cells populate the thymus and expand by cell division to generate a large population of immature thymocytes. The earliest thymocytes express neither CD4 nor CD8, and are therefore classed as double-negative ($CD4^-CD8^-$) cells. As they progress through their development, they become double-positive thymocytes ($CD4^+CD8^+$), and finally mature to single-positive ($CD4^+CD8^-$ or $CD4^-CD8^+$) thymocytes that are then released from the thymus to peripheral tissues.

[0100] About 98% of thymocytes die during the development processes in the thymus by failing either positive selection or negative selection, whereas the other 2% survive and leave the thymus to become mature immunocompetent T cells.

[0101] The double negative (DN) stage of the precursor T cell is focused on producing a functional β-chain whereas the double positive (DP) stage is focused on producing a functional α-chain, ultimately producing a functional αβ T cell receptor. As the developing thymocyte progresses through the four DN stages (DN1, DN2, DN3, and DN4), the T cell expresses an invariant α-chain but rearranges the β-chain locus. If the rearranged β-chain successfully pairs with the invariant α-chain, signals are produced which cease rearrangement of the β-chain (and silence the alternate allele) and result in proliferation of the cell. Although these signals require this pre-TCR at the cell surface, they are dependent on ligand binding to the pre-TCR. These thymocytes will then express both CD4 and CD8 and progresses to the double positive (DP) stage where selection of the α-chain takes place.

If a rearranged β-chain does not lead to any signaling (e.g. as a result of an inability to pair with the invariant α-chain), the cell may die by neglect (lack of signaling).

[0102] "Hematopoietic stem cells" or "HSC" have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, precursor cells that can give rise to myeloid cells such as, for example, macrophages, monocytes, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells and lymphoid lineages (such as, for example, T-cells, B-cells, NK-cells). HSCs have a heterogeneous population in which three classes of stem cells exist, which are distinguished by their ratio of lymphoid to myeloid progeny in the blood (L/M). In some alternatives described herein a host cell comprising a system of any one of the alternatives described herein is provided. In some alternatives of the host cells provided herein, the host cells are hematopoietic stem cells.

[0103] This disclosure provides for a system that has an inducible component for expression of transgenes and a constitutive component for expression of transgenes. The system can be tailored to provide for regulated expression of one or more transgenes to provide for functional characteristics in the transduced cells.

[0104] Although, T cell (CAR-T) adoptive therapy clinical trials (chimeric antigen receptor expressing T cells) can demonstrate potent anti-tumor activity, significant toxicities can arise, for example, by engraftment-induced cytokine storm (cytokine release syndrome), tumor lysis syndromes (TLS) and ongoing B cell cytopenias, each of which are attributable to unregulated functional outputs of constitutively expressed CARs. Such toxicities can threaten to limit the applicability of CAR-T cell adoptive therapy, in some patients. Clinical trials using transgene-modified adoptive T cell immunotherapies have tested T cells that can constitutively express the transgene, or are always in the "ON" state, contributing in large part to transgene associated side-effects. Methods to eliminate CAR-T cells such as suicide gene-mediated elimination of CAR-T cells, for example, can ameliorate such toxicities; however, this approach risks premature attenuation of anti-tumor activity and can significantly impact curative potential.

[0105] Current small molecule-regulated transgene expression technologies rely on a variety of drug inputs, which include, for example, macrolides, ecdysones and rapamycin analogs. However, use of these drugs may be limited due to the toxic off target

effects, unfavorable biodistribution and pharmacodynamics profiles, limited output dynamic range, and/or limited availability as FDA-approved commercially available pharmaceuticals. Furthermore, many of these systems use chimeric transcriptional regulators built from xenogeneic components, thus introducing the complication of immunogenicity when applying these systems to human therapeutics.

[0106] Small molecule regulated transgene expression is a highly sought technology in biomedicine, particularly in CAR T cell immunotherapy. Competing systems typically use chimeric transcription factors composed of xenogeneic domains and drug inducers that are not currently FDA approved.

[0107] As such, there is a need to identify methods for controlling chimeric receptor expression that are important for therapeutic activity and cell populations that will provide enhanced survival and efficacy *in vivo* while minimizing adverse side effects of the drugs that induce chimeric antigen receptor expression. There is also a need for expression systems and methods for modulating cells for use in cell therapy, such as for modulating expression of recombinant antigen receptors such as CARs and/or other molecules expressed by such cells, such as to improve therapeutic activity, enhance survival and/or efficacy *in vivo* and/or minimize adverse side effects. Described herein, are methods that surprisingly led to enhanced survival and efficacy of the treatments *in vivo*, with minimized adverse side effects.

[0108] In some alternatives, a transgene under the control of the inducible promoter, is provided. In some alternatives, the transgene encodes a chimeric antigen receptor (CAR). The inducible promoter provides for the capacity to terminate CAR expression in cells while providing for reactivation of the cells at a later date (e.g. in the case of relapse). In addition, the cycling of CAR T cells through on and off periods can minimize exhaustion and/or anergy due to chronic stimulation of the T cell receptors.

[0109] In some alternatives, a gene is under the control of the inducible promoter. In some alternatives, the gene encodes a chimeric cytokine receptor.

[0110] The design of the vectors also provides for additional transgenes that can enhance one or more functional characteristics of transduced cells, such as enhanced tumor potency, survival and proliferation of transduced cells. In some alternatives, these transgenes are under the control of an inducible promoter. Such transgenes include, without limitation,

genes that promote survival and proliferation, genes that prevent apoptosis, and genes that regulate checkpoint signaling. Such genes include genes encoding IL-2, IL-15, chemokine receptors, Bcl2, CA-Akt, dn-TGFbetaRIII, dn-SHP1/2, and/or PD-1CD28 chimeras. In some alternatives, the transgenes are genes encoding IL-2, IL-7, IL-15, chemokine receptors, Bcl2, chimeric cytokine receptors, CA-Akt, dn-TGFbetaRIII, dn-SHP1/2, and/or PD-1CD28 chimeras. In some alternatives, the gene that modulates checkpoint signaling, encodes a polypeptide that inhibits negative checkpoint regulators. In some alternatives, the negative checkpoint regulator comprises PD-1, VISTA, LAG-3 and/or TIM3. In some alternatives, the gene is under a control of an inducible promoter. In some alternatives, the gene under control of an inducible promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 88 (CCR(CD122) nucleotide sequence:

atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagattgtgatattgaaggtaaagatg
gcaaacaatatgagagtgttctaatggtcagcatcgatcaattattggacagcatgaaagaaattggtagcaattgcctgaataatgaatt
taacttttttaaaagacatatctgtgatgctaataaggaaggtatgtttttattccgtgctgctcgcaagttgaggcaatttcttaaaatgaata
gcactggtgattttgatctccacttattaaaagtttcagaaggcacaacaatactgttgaactgcactggccaggttaaaggaagaaaac
cagctgccctgggtgaagcccaaccaacaaagagtttggaagaaaataaatctttaaaggaacagaaaaaactgaatgacttgtgttt
cctaaagagactattacaagagataaaaacttgttggaataaaattttgatgggcactaaagaacacggaggcggtgggagcggagg
cggtgggagcatgacaattctaggtacaacttttggcatggtttttttctttacttcaagtcgtttctggagaaagtggctatgctcaaaatgg
agacttggaagatgcagaactggatgactactcattctcatgctatagccagttggaagtgaatggatcgcagcactcactgacctgtg
cttttgaggacccagatgtcaacatcaccaatctggaatttgaaatatgtggggccctcgtggaggtaaagtgcctgaatttcaggaaa
ctacaagagatatatttcatcgagacaaagaaattcttactgattggaaagagcaatatatgtgtgaaggttggagaaaagagtctaacc
tgcaaaaaaatagacctaaccactatagttaaacctgaggctccttttgacctgagtgtcatctatcgggaaggagccaatgactttgtg
gtgacatttaatacatcacacttgcaaaagaagtatgtaaaagttttaatgcacgatgtagcttaccgccaggaaaaggatgaaaacaa
atggacgcatgtgaatttatccagcacaaaactgacactcctgcagagaaagctccaaccggcagcaatgtatgagattaaagttcga
tccatccctgatcactattttaaaggcttctggagtgaatggagtccaagttattacttcagaactccagagatcaataatagctcagggg
agatggatcctatcttactaaccatcagcattttgagttttttctctgtcgctctgttggtcatcttggcctgtgtgttatggaactgcaggaac
accgggccatggctgaagaaggtcctgaagtgtaacaccccagacccctcgaagttcttttcccagctgagctcagagcatggagga
gacgtccagaagtggctctcttcgcccttcccctcatcgtccttcagccctggcggcctggcacctgagatctcgccactagaagtgct
ggagagggacaaggtgacgcagctgctcctgcagcaggacaaggtgcctgagcccgcatccttaagcagcaaccactcgctgacc
agctgcttcaccaaccagggttacttcttcttccacctcccggatgccttggagatagaggcctgccaggtgtactttacttacgacccct
actcagaggaagaccctgatgagggtgtggccggggcacccacagggtcttccccccaaccccctgcagcctctgtcaggggagga

cgacgcctactgcaccttcccctccagggatgacctgctgctcttctcccccagtctcctcggtggccccagcccccccaagcactgcc cctgggggcagtggggccggtgaagagaggatgcccccttctttgcaagaaagagtccccagagactgggaccccccagcccctgg ggcctcccaccccaggagtcccagacctggtggattttcagccacccccctgagctggtgctgcgagaggctggggaggaggtccct gacgctggccccagggagggagtcagtttcccctggtccaggcctcctgggcagggggagttcagggcccttaatgctcgcctgcc cctgaacactgatgcctacttgtccctccaagaactccagggtcaggacccaactcacttggtg). In some alternatives, the sequence under control of an inducible promoter encodes for an amino acid sequence set forth in SEQ ID NO: 89 (CCR(CD122) amino acid sequence: MLLLVTSLLLCELPHPAFLLIPDCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLN NEFNFFKRHICDANKEGMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCT GQVKGRKPAALGEAQPTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGT KEHGGGGSGGGGSMTILGTTFGMVFSLLQVVSGESGYAQNGDLEDAELDDYSFSCY SQLEVNGSQHSLTCAFEDPDVNITNLEFEICGALVEVKCLNFRKLQEIYFIETKKFLLI GKSNICVKVGEKSLTCKKIDLTTIVKPEAPFDLSVIYREGANDFVVTFNTSHLQKKYV KVLMHDVAYRQEKDENKWTHVNLSSTKLTLLQRKLQPAAMYEIKVRSIPDHYFKGF WSEWSPSYYFRTPEINNSSGEMDPILLTISILSFFSVALLVILACVLWNCRNTGPWLKK VLKCNTPDPSKFFSQLSSEHGGDVQKWLSSPFPSSSFSPGGLAPEISPLEVLERDKVTQ LLLQQDKVPEPASLSSNHSLTSCFTNQGYFFFHLPDALEIEACQVYFTYDPYSEEDPD EGVAGAPTGSSPQPLQPLSGEDDAYCTFPSRDDLLLFSPSLLGGPSPPSTAPGGSGAGE ERMPPSLQERVPRDWDPQPLGPPTPGVPDLVDFQPPPELVLREAGEEVPDAGPREGV SFPWSRPPGQGEFRALNARLPLNTDAYLSLQELQGQDPTHLV). In some alternatives, the sequence under control of an inducible promoter is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 89.

[0111] In some alternatives, the gene under control of an inducible promoter comprises the nucleic acid sequence set forth in SEQ ID NO: 90 (PD1ECD-IFNalpha nucleotide sequence nucleotide sequence: atgcagatccctcaggccccttggcctgtcgtgtgggctgtgctgcagctgggatggcggcctggctggtttctggacagccccgac agaccctggaaccccccctacattttcccctgccctgctggtcgtgaccgagggcgacaatgccaccttcacctgtagcttcagcaaca ccagcgagagcttcgtgctgaactggtacagaatgagccccagcaaccagaccgacaagctggccgccttccccgaggatagatct cagcccggccaggactgccggttcagagtgacccagctgcccaacggccgggacttccacatgtctgtcgtgcgggccagacgga acgacagcggcacatatctgtgcggcgccatcagcctggcccccaaggcccagatcaaagagagcctgagagccgagctgagag tgaccgagagaagggccgaagtgcctaccgcccaccctagcccatctccaagacctgccggccagttccagacactcgtgggcgg

aggatgcgacctgcctcagacacacagcctgggcagcagacggaccctgatgctgctggcccagatgcggaagatcagcctgttc agctgcctgaaggaccggcacgacttcggcttccctcaggaagagttcggcaaccagtttcagaaggccgagacaatccccgtgct gcacgagatgatccagcagatcttcaacctgttctccaccaaggacagcagcgccgcctgggacgagacactgctggacaagttcta caccgagctgtaccagcagctgaatgacctggaagcctgcgtgatccagggcgtgggcgtgacagagacacccctgatgaaggaa gatagcatcctggccgtgcgcaagtacttccagcggatcaccctgtacctgaaagagaagaagtacagcccctgcgcctgggaggt cgtgcgcgccgagatcatgagaagcttcagcctgagcaccaacctgcaggaaagcctgcggagcaaagaa). In some alternatives, the sequence under control of an inducible promoter encodes the amino acid sequence set forth in SEQ ID NO: 91 (PD1ECD-IFNalpha amino acid sequence: MQIPQAPWPVVWAVLQLGWRPGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSF SNTSESFVLNWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRVTQLPNGRDFHMSVVR ARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAGQFQTLV GGGCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIP VLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLM KEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE). In some alternatives, the sequence under control of an inducible promoter is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 91.

[0112] In some alternatives, the gene under control of an inducible promoter comprises the nucleic acid sequence set forth in SEQ ID NO: 92 (STAT5a nucleotide sequence:

atggcgggctggatccaggcccagcagctgcagggagacgcgctgcgccagatgcaggtgctgtacggccagcacttccccatcg aggtccggcactacttggcccagtggattgagagccagccatgggatgccattgacttggacaatccccaggacagagcccaagcc acccagctcctggagggcctggtgcaggagctgcagaagaaggcggagcaccaggtgggggaagatgggtttttactgaagatca agctggggcactacgccacgcagctccagaaaacatatgaccgctgccccctggagctggtccgctgcatccggcacattctgtaca atgaacagaggctggtccgagaagccaacaattgcagctctccggctgggatcctggttgacgccatgtcccagaagcaccttcaga tcaaccagacatttgaggagctgcgactggtcacgcaggacacagagaatgagctgaagaaactgcagcagactcaggagtacttc atcatccagtaccaggagagcctgaggatccaagctcagtttgcccagctggcccagctgagcccccaggagcgtctgagccggg agacggccctccagcagaagcaggtgtctctggaggcctggttgcagcgtgaggcacagacactgcagcagtaccgcgtggagct ggccgagaagcaccagaagaccctgcagctgctgcggaagcagcagaccatcatcctggatgacgagctgatccagtggaagcg gcggcagcagctggccgggaacggcgggcccccccgagggcagcctggacgtgctacagtcctggtgtgagaagttggccgagat catctggcagaaccggcagcagatccgcagggctgagcacctctgccagcagctgcccatccccggcccagtggaggagatgctg

gccgaggtcaacgccaccatcacggacattatctcagccctggtgaccagcacattcatcattgagaagcagcctcctcaggtcctga
agacccagaccaagtttgcagccaccgtacgcctgctggtgggcgggaagctgaacgtgcacatgaatccccccccaggtgaaggc
caccatcatcagtgagcagcaggccaagtctctgcttaaaaatgagaacacccgcaacgagtgcagtggtgagatcctgaacaactg
ctgcgtgatggagtaccaccaagccacgggcaccctcagtgcccacttcaggaacatgtcactgaagaggatcaagcgtgctgacc
ggcggggtgcagagtccgtgacagaggagaagttcacagtcctgtttgagtctcagttcagtgttggcagcaatgagcttgtgttcca
ggtgaagactctgtccctacctgtggttgtcatcgtccacggcagccaggaccacaatgccacggctactgtgctgtgggacaatgcc
tttgctgagccgggcagggtgccatttgccgtgcctgacaaagtgctgtggccgcagctgtgtgaggcgctcaacatgaaattcaag
gccgaagtgcagagcaaccggggcctgaccaaggagaacctcgtgttcctggcgcagaaactgttcaacaacagcagcagccacc
tggaggactacagtggcctgtccgtgtcctggtcccagttcaacagggagaacttgccgggctggaactacaccttctggcagtggtt
tgacggggtgatggaggtgttgaagaagcaccacaagccccactggaatgatggggccatcctaggttttgtgaataagcaacagg
cccacgacctgctcatcaacaagcccgacgggaccttcttgttgcgctttagtgactcagaaatcgggggcatcaccatcgcctggaa
gtttgattccccggaacgcaacctgtggaacctgaaaccattcaccacgcgggatttctccatcaggtccctggctgaccggctgggg
gacctgagctatctcatctatgtgtttcctgaccgccccaaggatgaggtcttctccaagtactacactcctgtgctggctaaagctgttg
atggatatgtgaaaccacagatcaagcaagtggtccctgagtttgtgaatgcatctgcagatgctgggggcagcagcgccacgtacat
ggaccaggccccctccccagctgtgtgcccccaggctccctataacatgtacccacagaaccctgaccatgtactcgatcaggatgg
agaattcgacctggatgagaccatggatgtggccaggcacgtggaggaactcttacgccgaccaatggacagtcttgactcccgcct
ctcgccccctgccggtcttttcacctctgccagaggctccctctca).

[0113] In some alternatives, the sequence under control of an inducible promoter encodes for the amino acid sequence set forth in SEQ ID NO: 93 (STAT5a amino acid sequence:

MAGWIQAQQLQGDALRQMQVLYGQHFPIEVRHYLAQWIESQPWDAIDLDNPQDRA
QATQLLEGLVQELQKKAEHQVGEDGFLLKIKLGHYATQLQKTYDRCPLELVRCIRHI
LYNEQRLVREANNCSSPAGILVDAMSQKHLQINQTFEELRLVTQDTENELKKLQQTQ
EYFIIQYQESLRIQAQFAQLAQLSPQERLSRETALQQKQVSLEAWLQREAQTLQQYR
VELAEKHQKTLQLLRKQQTIILDDELIQWKRRQQLAGNGGPPEGSLDVLQSWCEKL
AEIIWQNRQQIRRAEHLCQQLPIPGPVEEMLAEVNATITDIISALVTSTFIIEKQPPQVL
KTQTKFAATVRLLVGGKLNVHMNPPQVKATIISEQQAKSLLKNENTRNECSGEILNN
CCVMEYHQATGTLSAHFRNMSLKRIKRADRRGAESVTEEKFTVLFESQFSVGSNELV
FQVKTLSLPVVVIVHGSQDHNATATVLWDNAFAEPGRVPFAVPDKVLWPQLCEALN
MKFKAEVQSNRGLTKENLVFLAQKLFNNSSSHLEDYSGLSVSWSQFNRENLPGWNY
TFWQWFDGVMEVLKKHHKPHWNDGAILGFVNKQQAHDLLINKPDGTFLLRFSDSEI

GGITIAWKFDSPERNLWNLKPFTTRDFSIRSLADRLGDLSYLIYVFPDRPKDEVFSKY YTPVLAKAVDGYVKPQIKQVVPEFVNASADAGGSSATYMDQAPSPAVCPQAPYNM YPQNPDHVLDQDGEFDLDETMDVARHVEELLRRPMDSLDSRLSPPAGLFTSARGSLS). In some alternatives, the sequence under control of an inducible promoter is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 93.

[0114] In some alternatives, the gene under control of an inducible promoter comprises the nucleic acid sequence set forth in SEQ ID NO: 94 (Constitutively active-STAT5a nucleotide sequence:
atggcgggctggatccaggcccagcagctgcagggagacgcgctgcgccagatgcaggtgctgtacggccagcacttccccatcg
aggtccggcactacttggcccagtggattgagagccagccatgggatgccattgacttggacaatccccaggacagagcccaagcc
acccagctcctggagggcctggtgcaggagctgcagaagaaggcggagcaccaggtgggggaagatgggtttttactgaagatca
agctggggcactacgccacgcagctccagaaaacatatgaccgctgccccctggagctggtccgctgcatccggcacattctgtaca
atgaacagaggctggtccgagaagccaacaattgcagctctccggctgggatcctggttgacgccatgtcccagaagcaccttcaga
tcaaccagacatttgaggagctgcgactggtcacgcaggacacagagaatgagctgaagaaactgcagcagactcaggagtacttc
atcatccagtaccaggagagcctgaggatccaagctcagtttgcccagctggcccagctgagcccccaggagcgtctgagccggg
agacggccctccagcagaagcaggtgtctctggaggcctggttgcagcgtgaggcacagacactgcagcagtaccgcgtggagct
ggccgagaagcaccagaagaccctgcagctgctgcggaagcagcagaccatcatcctggatgacgagctgatccagtggaagcg
gcggcagcagctggccgggaacggcgggcccccccgagggcagcctggacgtgctacagtcctggtgtgagaagttggccgagat
catctggcagaaccggcagcagatccgcagggctgagcgcctctgccagcagctgcccatccccggcccagtggaggagatgct
ggccgaggtcaacgccaccatcacggacattatctcagccctggtgaccagcacattcatcattgagaagcagcctcctcaggtcctg
aagacccagaccaagtttgcagccaccgtacgcctgctggtgggcgggaagctgaacgtgcacatgaatcccccccaggtgaagg
ccaccatcatcagtgagcagcaggccaagtctctgcttaaaaatgagaacacccgcaacgagtgcagtggtgagatcctgaacaact
gctgcgtgatggagtaccaccaagccacgggcaccctcagtgcccacttcaggaacatgtcactgaagaggatcaagcgtgctgac
cggcggggtgcagagtccgtgacagaggagaagttcacagtcctgtttgagtctcagttcagtgttggcagcaatgagcttgtgttcca
ggtgaagactctgtccctacctgtggttgtcatcgtccacggcagccaggaccacaatgccacggctactgtgctgtgggacaatgcc
tttgctgagccgggcagggtgccatttgccgtgcctgacaaagtgctgtggccgcagctgtgtgaggcgctcaacatgaaattcaag
gccgaagtgcagagcaaccggggcctgaccaaggagaacctcgtgttcctggcgcagaaactgttcaacaacagcagcagccacc
tggaggactacagtggcctgtccgtgtcctggtcccagttcaacagggagaacttgccgggctggaactacaccttctggcagtggtt
tgacggggtgatggaggtgttgaagaagcaccacaagccccactggaatgatggggccatcctaggttttgtgaataagcaacagg
cccacgacctgctcatcaacaagcccgacgggaccttcttgttgcgctttagtgactcagaaatcgggggcatcaccatcgcctggaa

gtttgattccccggaacgcaacctgtggaacctgaaaccattcaccacgcgggatttctccatcaggtccctggctgaccggctgggg gacctgagctatctcatctatgtgtttcctgaccgccccaaggatgaggtcttctccaagtactacactcctgtgctggctaaagctgttg atggatatgtgaaaccacagatcaagcaagtggtccctgagtttgtgaatgcatttgcagatgctgggggcagcagcgccacgtacat ggaccaggccccctccccagctgtgtgcccccaggctccctataacatgtacccacagaaccctgaccatgtactcgatcaggatgg agaattcgacctggatgagaccatggatgtggccaggcacgtggaggaactcttacgccgaccaatggacagtcttgactcccgcct ctcgccccctgccggtcttttcacctctgccagaggctccctctca).

[0115] In some alternatives, the sequence under control of an inducible promoter encodes for the amino acid sequence set forth in SEQ ID NO: 95 (Constitutively active-STAT5a amino acid sequence: MAGWIQAQQLQGDALRQMQVLYGQHFPIEVRHYLAQWIESQPWDAIDLDNPQDRA QATQLLEGLVQELQKKAEHQVGEDGFLLKIKLGHYATQLQKTYDRCPLELVRCIRHI LYNEQRLVREANNCSSPAGILVDAMSQKHLQINQTFEELRLVTQDTENELKKLQQTQ EYFIIQYQESLRIQAQFAQLAQLSPQERLSRETALQQKQVSLEAWLQREAQTLQQYR VELAEKHQKTLQLLRKQQTIILDDELIQWKRRQQLAGNGGPPEGSLDVLQSWCEKL AEIIWQNRQQIRRAERLCQQLPIPGPVEEMLAEVNATITDIISALVTSTFIIEKQPPQVL KTQTKFAATVRLLVGGKLNVHMNPPQVKATIISEQQAKSLLKNENTRNECSGEILNN CCVMEYHQATGTLSAHFRNMSLKRIKRADRRGAESVTEEKFTVLFESQFSVGSNELV FQVKTLSLPVVVIVHGSQDHNATATVLWDNAFAEPGRVPFAVPDKVLWPQLCEALN MKFKAEVQSNRGLTKENLVFLAQKLFNNSSSHLEDYSGLSVSWSQFNRENLPGWNY TFWQWFDGVMEVLKKHHKPHWNDGAILGFVNKQQAHDLLINKPDGTFLLRFSDSEI GGITIAWKFDSPERNLWNLKPFTTRDFSIRSLADRLGDLSYLIYVFPDRPKDEVFSKY YTPVLAKAVDGYVKPQIKQVVPEFVNAFADAGGSSATYMDQAPSPAVCPQAPYNM YPQNPDHVLDQDGEFDLDETMDVARHVEELLRRPMDSLDSRLSPPAGLFTSARGSLS). In some alternatives, the sequence under control of an inducible promoter is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 95.

[0116] In some alternatives, the gene under control of an inducible promoter comprises the nucleic acid sequence set forth in SEQ ID NO: 96 (Dominant negative TGFbRII nucleotide sequence: atgggtcgggggctgctcaggggcctgtggccgctgcacatcgtcctgtggacgcgtatcgccagcacgatcccaccgcacgttca gaagtcggttaataacgacatgatagtcactgacaacaacggtgcagtcaagtttccacaactgtgtaaattttgtgatgtgagattttcc

acctgtgacaaccagaaatcctgcatgagcaactgcagcatcacctccatctgtgagaagccacaggaagtctgtgtggctgtatgga
gaaagaatgacgagaacataacactagagacagtttgccatgaccccaagctcccctaccatgactttattctggaagatgctgcttct
ccaaagtgcattatgaaggaaaaaaaaaaagcctggtgagactttcttcatgtgttcctgtagctctgatgagtgcaatgacaacatcatct
tctcagaagaatataacaccagcaatcctgacttgttgctagtcatatttcaagtgacaggcatcagcctcctgccaccactgggagttg
ccatatctgtcatcatcatcttctactgctaccgcgttaaccggcagcagaagctgagttcaacctgggaaaccggcaagacgcggaa
gctcatggagttcagcgagcactgtgccatcatcctggaagatgaccgctctgacatcagctccacgtgtgccaacaacatcaaccac
aacacagagctgctgcccattgagctggacaccctggtggggaaaggtcgctttgctgaggtctataaggccaagctgaagcagaa
cacttcagagcagtttgagacagtggcagtcaagatcttt).

[0117] In some alternatives, the sequence under control of an inducible promoter encodes for the amino acid sequence set forth in SEQ ID NO: 97 (Dominant negative TGFbRII amino acid sequence: MGRGLLRGLWPLHIVLWTRIASTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDV RFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILE DAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDLLLVIFQVTGISLLP PLGVAISVIIIFYCYRVNRQQKLSSTWETGKTRKLMEFSEHCAIILEDDRSDISSTCAN NINHNTELLPIELDTLVGKGRFAEVYKAKLKQNTSEQFETVAVKIF). In some alternatives, the sequence under control of an inducible promoter is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 97.

[0118] In some alternatives, the gene under control of an inducible promoter comprises the nucleic acid sequence set forth in SEQ ID NO: 98 (Dominant negative SHP1 nucleotide sequence: atggtgaggtggtttcaccgagacctcagtgggctggatgcagagaccctgctcaagggccgaggtgtccacggtagcttcctggct cggcccagtcgcaagaaccagggtgacttctcgctctccgtcagggtgggggatcaggtgacccatattcggatccagaactcagg ggatttctatgacctgtatggaggggagaagtttgcgactctgacagagctggtggagtactacactcagcagcagggtgtcctgcag gaccgcgacggcaccatcatccacctcaagtacccgctgaactgctccgatcccactagtgagaggtggtaccatggccacatgtct ggcgggcaggcagagacgctgctgcaggccaagggcgagccctggacgtttcttgtgcgtgagagcctcagccagcctggagact tcgtgctttctgtgctcagtgaccagcccaaggctggcccaggctccccgctcagggtcacccacatcaaggtcatgtgcgagggtg gacgctacacagtgggtggtttggagaccttcgacagcctcacggacctggtggagcatttcaagaagacggggattgaggaggcc tcaggcgcctttgtctacctgcggcagccgtactatgccacgagggtgaatgcggctgacattgagaaccgagtgttggaactgaac aagaagcaggagtccgaggatacagccaaggctggcttctgggaggagtttgagagtttgcagaagcaggaggtgaagaacttgc

accagcgtctggaagggcagcggccagagaacaagggcaagaaccgctacaagaacattctccccttgaccacagccgagtgat
cctgcagggacgggacagtaacatccccgggtccgactacatcaatgccaactacatcaagaaccagctgctaggccctgatgaga
acgctaagacctacatcgccagccagggctgtctggaggccacggtcaatgacttctggcagatggcgtggcaggagaacagccgt
gtcatcgtcatgaccacccgagaggtggagaaaggccggaacaaatgcgtcccatactggcccgaggtgggcatgcagcgtgctta
tgggccctactctgtgaccaactgcggggagcatgacacaaccgaatacaaactccgtaccttacaggtctccccgctggacaatgg
agacctgattcgggagatctggcattaccagtacctgagctggcccgaccatggggtccccagtgagcctgggggtgtcctcagctt
cctggaccagatcaaccagcggcaggaaagtctgcctcacgcagggcccatcatcgtgcactccagcgccggcatcggccgcaca
ggcaccatcattgtcatcgacatgctcatggagaacatctccaccaagggcctggactgtgacattgacatccagaagaccatccaga
tggtgcgggcgcagcgctcgggcatggtgcagacggaggcgcagtacaagttcatctacgtggccatcgcccagttcattgaaacc
actaagaagaagctggaggtcctgcagtcgcagaagggccaggagtcggagtacgggaacatcacctatcccccagccatgaaga
atgcccatgccaaggcctcccgcacctcgtccaaacacaaggaggatgtgtatgagaacctgcacactaagaacaagagggagga
gaaagtgaagaagcagcggtcagcagacaaggagaagagcaagggttccctcaagaggaagtga).

[0119] In some alternatives, the sequence under control of an inducible promoter encodes for the amino acid sequence set forth in SEQ ID NO: 99: Dominant negative SHP1 amino acid sequence: MVRWFHRDLSGLDAETLLKGRGVHGSFLARPSRKNQGDFSLSVRVGDQVTHIRIQN SGDFYDLYGGEKFATLTELVEYYTQQQGVLQDRDGTIIHLKYPLNCSDPTSERWYH GHMSGGQAETLLQAKGEPWTFLVRESLSQPGDFVLSVLSDQPKAGPGSPLRVTHIKV MCEGGRYTVGGLETFDSLTDLVEHFKKTGIEEASGAFVYLRQPYYATRVNAADIEN RVLELNKKQESEDTAKAGFWEEFESLQKQEVKNLHQRLEGQRPENKGKNRYKNILP FDHSRVILQGRDSNIPGSDYINANYIKNQLLGPDENAKTYIASQGCLEATVNDFWQM AWQENSRVIVMTTREVEKGRNKCVPYWPEVGMQRAYGPYSVTNCGEHDTTEYKLR TLQVSPLDNGDLIREIWHYQYLSWPDHGVPSEPGGVLSFLDQINQRQESLPHAGPIIV HSSAGIGRTGTIIVIDMLMENISTKGLDCDIDIQKTIQMVRAQRSGMVQTEAQYKFIY VAIAQFIETTKKKLEVLQSQKGQESEYGNITYPPAMKNAHAKASRTSSKHKEDVYEN LHTKNKREEKVKKQRSADKEKSKGSLKRK). In some alternatives, the sequence under control of an inducible promoter is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 99.

[0120] In some alternatives, the gene under control of an inducible promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 100 (PD1TM-MyD88 nucleotide sequence:

atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaggcggaggagtgggagtcgtggg
cggactgctgggatctctggtgctgctcgtgtgggtgctggccgtgattggcggaggaatggctgctggcggacctggcgctggatc
tgctgctcctgtgtctagcaccagcagcctgcctctggccgccctgaatatgagagtgcggcggagactgagcctgttcctgaacgtg
cggacacaggtggccgccgattggacagctctggccgaggaaatggacttcgagtacctggaaatccggcagctggaaacccagg
ccgaccctacaggacgcctgctggatgcttggcagggcagaccaggcgcttctgtggggagactgctggaactgctgaccaagctg
ggccgggacgacgtgctgctggaactgggccctagcatcgaagaggactgccagaagtacatcctgaagcagcagcaggaagag
gccgagaagcctctgcaggtggcagccgtggatagcagcgtgccaagaacagctgagctggccggaatcaccaccctggacgat
cctctgggccacatgcccgagagattcgacgccttcatctgctactgccccagcgacatccagttcgtgcaggaaatgatcagacag
ctggaacagaccaactaccggctgaagctgtgcgtgtccgaccgggatgtgctgcctggcacctgtgtgtggtctatcgccagcgag
ctgatcgagaagcggtgcagacggatggtcgtggtggtgtccgacgactacctgcagtccaaagagtgcgacttccagaccaagttc
gccctgagcctgagccctggcgcccaccagaagagactgatccccatcaagtacaaggccatgaagaaagagttccccagcatcct
gcggttcatcaccgtgtgcgactacaccaacccctgcaccaagtcctggttctggaccagactggccaaggccctgtctctgcct).

In some alternatives, the gene under control of an inducible promoter encodes for an amino acid sequence set forth in SEQ ID NO: 101 (PD1TM-MyD88 amino acid sequence: MLLLVTSLLLCELPHPAFLLIPGGGVGVVGGLLGSLVLLVWVLAVIGGGMAAGGPG AGSAAPVSSTSSLPLAALNMRVRRRLSLFLNVRTQVAADWTALAEEMDFEYLEIRQL ETQADPTGRLLDAWQGRPGASVGRLLELLTKLGRDDVLLELGPSIEEDCQKYILKQQ QEEAEKPLQVAAVDSSVPRTAELAGITTLDDPLGHMPERFDAFICYCPSDIQFVQEMI RQLEQTNYRLKLCVSDRDVLPGTCVWSIASELIEKRCRRMVVVVSDDYLQSKECDF QTKFALSLSPGAHQKRLIPIKYKAMKKEFPSILRFITVCDYTNPCTKSWFWTRLAKAL SL). In some alternatives, the sequence under control of an inducible promoter is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 101.

[0121] The disclosure provides for a system comprising first and second nucleic acids, and vectors and host cells including such nucleic acids. Each of the first and second nucleic acids comprise a number of modular components that can be excised and replaced with other components in order to customize the system for a specific target cell. In some alternatives, the first nucleic acid includes an inducible promoter for control of the expression of the genes (e.g., polynucleotide coding for a chimeric antigen receptor) in an on and off manner as needed, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a

wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In other alternatives, the second nucleic acid comprises a constitutive promoter that provides for expression of a transcriptional activator. In some alternatives, the gene encodes for a chimeric antigen receptor. In some alternatives, the gene encodes for a chimeric antigen receptor AND a transcriptional activator (encoded by one plasmid).

Inducible System.

[0122] The disclosure provides a system useful for providing regulated expression of transgenes in cells, such as mammalian cells. Such transgenes include, without limitation, T cell receptors, affinity matured T cell receptors, chimeric antigen receptors, chemokine receptors, chimeric chemokine receptors, cytokines, genes that inhibit apoptosis, and/or genes that modulate checkpoint signaling. In some alternatives, the polypeptide that modulates checkpoint signaling inhibits negative checkpoint regulators. In some alternatives, the negative checkpoint regulator comprises PD-1, VISTA, LAG-3 and/or TIM3. In some alternatives, the system contains a number of modular components that provide for easy substitution of elements of the nucleic acid. In some alternatives of the system, the system provides regulation of expression of transgenes in cells, such as mammalian cells, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives, the transgenes code for T cell receptors, affinity matured T cell receptors, chimeric antigen receptors, chemokine receptors, chimeric chemokine receptors, cytokines, genes that regulate apoptosis, and/or genes that modulate checkpoint signaling. In some alternatives, the gene that modulates checkpoint signaling encodes a polypeptide inhibits negative checkpoint regulators. In some alternatives, the negative checkpoint regulator comprises PD-1, VISTA, LAG-3 and/or TIM3.

[0123] In some alternatives, a system for inducible expression of a transgene is provided. In some alternatives, the transgene encodes a chimeric antigen receptor. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, is provided. In some alternatives, a system for inducible expression of a

chimeric antigen receptor in cells, such as mammalian cells, comprises: a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor which comprises a ligand binding domain that is specific for a ligand selected from a tumor specific molecule, viral molecule, or any other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain, and a fourth polynucleotide, which encodes an intracellular signaling domain, and a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives, the second promoter is constitutive or inducible.

[0124] In some alternatives, a polynucleotide coding for a chimeric antigen receptor comprises a polynucleotide coding for a ligand binding domain, wherein the target molecule is a tumor specific antigen, a polynucleotide coding for a polypeptide spacer wherein the spacer is optionally optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide coding for an intracellular signaling domain. In some alternatives, an expression vector comprises a first and/or second nucleic acid, as described herein. Polypeptides encoded by all of or a portion of the chimeric receptor nucleic acids are also included herein.

[0125] In other alternatives, a first nucleic acid comprises a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a polynucleotide coding for a gene that promotes cell survival and proliferation, a gene that regulates apoptosis, and/or a gene that modulates checkpoint signaling. Such genes include genes encoding IL-2, IL-7, IL-15, chemokine receptors, chimeric chemokine receptors, Bcl2, CA-Akt, dn-TGFbetaRIII, dn-SHP1/2, and/or PD-1CD28 chimeras. In some alternatives, the gene that modulates checkpoint signaling encodes a polypeptide that inhibits negative

checkpoint regulators. In some alternatives, the negative checkpoint regulator comprises PD-1, VISTA, LAG-3 and/or TIM3.

[0126] In some alternatives, the system is for inducible expression of a gene that regulates a T cell function.

Inducible Promoters.

[0127] A system comprises a first nucleic acid comprising a first promoter inducible by a drug. By utilizing an inducible promoter, transgene expression can be turned on and off in order to avoid toxic side effects and/or to allow the cells to rest during remission. Another purpose of the inducible promoter system is to improve anti-tumor efficacy by turning on genes that enhance T cell function. Although several inducible promoter systems are known, clinical applicability of these systems is limited due to toxic off target effects, unfavorable biodistribution and pharmacodynamics profiles, limited output dynamic range, and/or limited availability as FDA-approved commercially available pharmaceuticals. Furthermore, many of these systems use chimeric transcriptional regulators built from xenogeneic components, thus introducing the complication of immunogenicity when applying these systems to human therapeutics. In some alternatives, the first nucleic acid comprises a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral specific molecule, and other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain.

[0128] In some alternatives, a first promoter is inducible by a drug. The drug is selected based on safety record, favorable pharmacokinetic profile, tissue distribution, a low partition coefficient between the extracellular space and cytosol, low immunogenicity, low toxicities, and/or high expression in lymphocytes. In a specific alternative, a drug is selected that is FDA approved, provides for transgene expression in lymphocytes, does not activate other undesirable gene expression, and induces a promoter that does not contain any xenogeneic components. In some alternatives, the inducible promoter is activated by a

transcriptional activator that interacts with a drug. The transcriptional activator is activated or able to bind to and activate the inducible promoter in the presence of the drug.

[0129] A specific alternative of a drug is a drug that binds to an estrogen receptor ligand binding domain of a transcriptional activator. In some alternatives, the drug includes tamoxifen, its metabolites, analogs, and pharmaceutically acceptable salts and/or hydrates or solvates thereof. In some alternatives, the drug includes tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8.

[0130] Tamoxifen, CAS RN: 10540-29-1, useful in some approaches described herein, is also known as 2-(4-((1Z)-1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl-ethanamine, or (Z)-2-(para-(1,2-Diphenyl-1-butenyl)phenoxy)-N,N-dimethylamine (IUPAC), and has a molecular formula of $C_{26}H_{29}NO$ and a molecular weight (M.W.) of 371.52 g/mol. Tamoxifen is a Selective Estrogen Receptor Modulator with tissue-specific activities. Tamoxifen acts as an anti-estrogen (inhibiting agent) agent in the mammary tissue, but as an estrogen (stimulating agent) in cholesterol metabolism, bone density, and cell proliferation in the endometrium. Tamoxifen is frequently administered orally as a pharmaceutically acceptable salt. For example, Tamoxifen citrate (RN 54965-24-1, M.W. 563.643) is indicated for treatment of metastatic breast cancer, and as an adjuvant for the treatment of breast cancer in women following mastectomy axillary dissection, and breast irradiation. Tamoxifen citrate is also indicated to reduce incidence of breast cancer in women at high risk for breast cancer.

[0131] Metabolites of tamoxifen in rat, mouse and human breast cancer patients, useful in some approaches described herein, include major metabolites N-desmethyltamoxifen (RN 31750-48-8, M.W. 357.494) and 4-hydroxytamoxifen (4-OHT) (RN 68392-35-8, M.W. 387.52, Afimoxifene), and are disclosed in Robinson *et al.* (Metabolites, pharmacodynamics, and pharmacokinetics of tamoxifen in rats and mice compared to the breast cancer patient. Drug Metab Dispos January 1991 19:36-43; incorporated by reference in its entirety herein). Additional cytochrome P-450 metabolites, useful in some approaches described herein, include cis-4-hydroxytamoxifen (RN 174592, M.W. 387.52; Afimoxifene, E-isomer), and 4'-hydroxytamoxifen ((Z)-4-(1-(4-(2-(dimethylamino)ethoxy)phenyl)-1-phenylbut-1-en-2-yl)phenol) as disclosed in Crewe *et al.* (Metabolism of Tamoxifen by recombinant human cytochrome P-450 enzymes: Formation of

the 4-hydroxy, 4'-hydroxy and N-desmethyl metabolites and isomerization of trans-4-hydroxytamoxifen, Drug Metab Dispos, 30(8): 869-874, 2002, FIG. 1; incorporated by reference in its entirety herein).

[0132] Compounds with structural similarity to tamoxifen, useful in some approaches described herein, include, but are not limited to, cis-tamoxifen (RN 13002-65-8, M.W. 371.521), 4-methyltamoxifen (RN 73717-95-5, M.W. 385.548), N-desmethyltamoxifen (RN 31750-48-8, M.W. 357.494), (Z)-desethyl methyl tamoxifen (RN 15917-50-7, M.W. 357.494), (E)-desethyl methyl tamoxifen (RN 31750-45-5, M.W. 357.494), trans-4-hydoxytamoxifen (RN 68047-06-3, M.W. 387.52), Afimoxifene (RN 68392-35-8, M.W. 387.52, 4-hydroxytamoxifen), Afimoxifene, E-isomer (RN 174592-47-3, M.W. 387.52), 4-chlorotamoxifen (RN 77588-46-6, M.W. 405.966), 4-fluorotamoxifen (RN 73617-96-6, M.W. 389.511), Toremifene (RN 89778-26-7, M.W. 405.966), desethyl tamoxifen (RN 19957-51-8, M.W. 343.47), (E)-desethyl tamoxifen (RN 97151-10-5, M.W. 343.47), (Z)-desethyl tamoxifen (RN 97151-11-6, M.W. 343.47), Miproxifene (RN 129612-87-9, M.W. 429.6), 2-(p-(beta-ethyl-alpha-phenylstyryl)phenoxy)triethylamine (RN 749-86-0, M.W. 399.575), Droloxifene (RN 82413-20-5, M.W. 387.52), 4-iodo-tamoxifen (RN 116057-68-2, M.W. 497.413), dihydrotamoxifen (RN 109640-20-2, M.W. 373.537), (E)-N,N-dimethyl-2-(4-(1-(2-methylphenyl)-2-phenyl-1-butenyl)phenoxy)ethanamine (RN 97150-96-4, M.W. 385.548), or 4-hydroxytoremifene (RN 110503-62-3, M.W. 421.965); and/or pharmaceutically acceptable salts and/or hydrates or solvates thereof.

[0133] For example, citrate salts of tamoxifen, or citrate salts of compounds with structural similarity to tamoxifen, useful in some approaches described herein, include, but are not limited to tamoxifen citrate (RN 54965-24-1, M.W. 563.64), 2-(p-(1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethylethylamine citrate (RN 7244-97-5, 563.64), (E)-tamoxifen citrate (RN 76487-65-5, M.W. 563.64), Toremifene citrate (RN 89778-27-8, M.W. 598.088), Droloxifene citrate (RN 97752-20-0, M.W. 579.64), 2-(p-(1,2-bis(p-methoxyphenyl)-1-butenyl)phenoxy)triethylamine citrate (RN 42920-39-8, M.W. 651.748), 2-(4-(1,2-diphenylethenyl)phenoxy)-N,N-diethyl-ethanamine 2-hydroxy-1,2,3-propanetricarboxylate (RN 40297-42-5, M.W. 563.643), 2-(p-(alpha-phenylstyryl)phenoxy)triethylamine citrate (RN 102433-95-4, M.W. 563.64), 2-(p-(2-(p-methoxyphenyl)-1-phenyl-1-butenyl)phenoxy)triethylamine citrate (1:1) (RN 42824-34-0, M.W. 637.72), 2-(p-(1-(p-

methoxyphenyl)-2-phenylpropenyl)phenoxy)triethylamine citrate (RN 13554-24-0, M.W. 607.696), 2-(p-(alpha-(p-methoxyphenyl)styryl)phenoxy)triethylamine citrate monohydrate (RN 13542-71-7, M.W. 593.669), 2-(p-(p-methoxy-alpha-phenylphenethyl) phenoxy)triethylamine citrate (RN 16421-72-0, M.W. 595.685), alpha-(p-(2-(diethylamino)ethoxy)phenyl)-beta-ethyl-p-methoxy-alpha-phenylphenethyl alcohol citrate (1:1) (RN 35263-93-5, M.W. 639.737), 1-(p-(2-(diethylamino)ethoxy)phenyl)-2-(p-methoxyphenyl)-1-phenylethanol citrate (M.W. 611.68), alpha-p-(2-(diethylamino)ethoxy)phenyl)-beta-ethyl-alpha-(p-hydroxyphenyl)-p-methoxyphenethyl alcohol citrate (RN 35263-96-8, M.W. 655.737), and/or 2-(p-(p-methoxy-alpha-methylphenethyl)phenoxy)-triethylamine citrate (RN 15624-34-7, M.W. 533.614).

[0134] In some alternatives, an effective amount of the drug for inducing expression is an amount that provides for an increase in transgene expression over uninduced and/or basal level of expression. In some alternatives, this amount can be readily determined using known dosages and pharmacokinetic profile of the drug. In the systems provided herein, wherein the systems are inducible by the drug, the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor.

[0135] In some alternatives, the inducible promoter has a low level of basal activity. When a lentiviral vector is used, the level of basal activity in uninduced cells is 20%, 15%, 10%, 5%, 4%, 3%, 2%, 1% or less, or any level of basal activity in between a range defined by any two aforementioned values, as compared to when cells are induced to express the gene. The level of basal activity can be determined by measuring the amount of the expression of the transgene (e.g. marker gene) in the absence of the inducer (e.g. drug) using flow cytometry.

[0136] In some alternatives, the inducible promoter provides for a high level of induced activity, as compared to uninduced or basal activity. In some alternatives, the level of activity in the induced state is 2, 4, 6, 8, or 10 fold or greater than the activity level in the uninduced state. In some alternatives, transgene expression under control of the inducible promoter is turned off in the absence of a transactivator in less than 10, 8, 6, 4, 2, or 1 days excluding 0 days.

[0137] In some alternatives, an inducible promoter can be designed and/or modified to provide for a low level of basal activity, a high level of inducibility, and/or a short time for reversibility. In some alternatives, the inducible promoter is the 7xHBD/mE1b promoter. An exemplary sequence for the promoter is set forth in SEQ ID NO: 23 (SEQ ID NO: 23; tagttaataatctacaatagttaataatctacaatagttaataatctacaatagttaataatctacaatagttaataatctacaatagttaataatctacaatagttaataatctacaatagttaataatctacaagagctcagggtatataatg). For example, in the 7xHBD/mE1b promoter, mutations can be made to enhance the binding of the transcriptional activator. In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values.

[0138] In some alternatives, the system employs a synthetic transcriptional activator which, in the presence of the drug (e.g., tamoxifen), binds a synthetic promoter upstream of a transgene to induce expression. In some alternatives, the transcriptional activator is HEA3. An exemplary amino acid sequence is set forth in SEQ ID NO: 1 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FKSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP

KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADM
DFSALLSQISS). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 1. The mutant tamoxifen-specific ligand binding domain of the estrogen receptor ligand binding domain (ER-LBD) is found at amino acids 282-595 of the TamR-tf and has a mutation at position 521. The p65 activation domain of NF-κB (p65 or TAD) is found at amino acids 596 to 862. SEQ ID NO: 1 comprises one point mutation in the ER-LBD that ablates binding to endogenous estrogen, but confers nanomolar specificity to 4-OHT, fulvestrant and other estrogen analogs.

[0139] In some alternatives, the HEA3 transcription factor comprises at least one point mutation that ablates binding to the endogenous estrogen but confers nanomolar specificity tamoxifen metabolite, 4-hydroxytamoxifen, fulvestrant, and other estrogen analogs. In some alternatives, the one point mutation is at position 521 of the sequence of the wild-type HEA3. In some alternatives, the amino acid sequence comprises a sequence set forth in SEQ ID NO: 1 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FKSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADM
DFSALLSQISS). SEQ ID NO: 1 comprises one point mutation in the ER-LBD that ablates

binding to endogenous estrogen, but confers nanomolar specificity to 4-OHT, fulvestrant and other estrogen analogs.

[0140] In some alternatives, the HEA3 transcription factor comprises at least one point mutation in the p65 domain that enhances transcriptional activity. In some alternatives, the point mutation is at position 846 of the sequence of the wild-type HEA3 (position 536 in the RelA protein, which correspond to position 846 in HEA3). In some alternatives, the amino acid sequence comprises a sequence set forth in SEQ ID NO: 2 (SEQ ID NO: 2; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FKSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM DFSALLSQISS). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 2. SEQ ID NO: 2 comprises a point mutation in HEA3, in the p65 domain which enhances transcriptional activity and is referred to as HEA3 (p65/S536E). The p65/S536E position in the RelA protein corresponds to position 846 in wild type HEA3 and wild type HEA4.

[0141] In some alternatives, the HEA3 transcription factor comprises at least one point mutation in the p65 domain that enhances transcriptional activity. In some alternatives, the point mutation is at position 621 of the sequence of the wild-type HEA3 (This is position 310 of the WT RelA protein). In some alternatives, the amino acid sequence comprises a

sequence set forth in SEQ ID NO: 3 (SEQ ID NO: 3; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADM DFSALLSQISS). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 3. SEQ ID NO: 3 comprises a sequence of HEA3 containing one point mutation (K310Q positions in the RelA protein) in the p65 domain that enhances transcriptional activity. This is referred to as HEA3 (p65/K310Q). K310Q refers to position 310 of RelA. This position thus corresponds to position 621 of WT HEA3 AND WT HEA4.

[0142] In some alternatives, the HEA3 transcription factor comprises at least three point mutations in the estrogen receptor ligand binding domain that ablates binding to endogenous estrogen, and confer nanomolar sensitivity to CMP8 and 4-hydroxytamoxifen. In some alternatives, the point mutations are at positions 384, 421 and 521 of the sequence of the wild-type HEA3. In some alternatives, the amino acid sequence comprises a sequence set forth in SEQ ID NO: 8 (SEQ ID NO: 8; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR

KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWMEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGGVEIFDMLLATSSRFRMMNLQGEEFVCL
KSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLAQ
LLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVEE
TDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYETF
KSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFPS
GQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAPK
PTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIPV
APHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADMDF
SALLSQISS). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 8. SEQ ID No: 8 comprises the sequence of HEA3 containing three point mutations (L384M, M421G, G521R) in the ER-LBD that ablate binding to endogenous estrogen, and confer nanomolar sensitivity to CMP8 and 4-hydroxytamoxifen. This is referred to as CMP8-HEA3.

[0143] In some alternatives, the HEA3 transcription factor is a CMP8-responsive HEA3 transcription factor. In some alternatives, the CMP8-responsive HEA3 transcription factor comprises at least one point mutation in the p65 domain that enhances transcriptional activity. In some alternatives, the point mutation is at position 846 of the sequence of the CMP8-responsive HEA3 (position 536 in the RelA protein, which correspond to position 846 in HEA3). In some alternatives, the amino acid sequence comprises a sequence set forth in SEQ ID NO: 9 (SEQ ID NO: 9;
MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWMEILMIGLV

WRSMEHPGKLLFAPNLLLDRNQGKCVEGGVEIFDMLLATSSRFRMMNLQGEEFVCL
KSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLAQ
LLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVEE
TDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYETF
KSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFPS
GQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAPK
PTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIPV
APHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADMDF
SALLSQISS). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 9. SEQ ID NO: 9 is the sequence of CMP8-HEA3 containing one point mutation (S536E) in the p65 domain that enhances transcriptional activity. This is referred to as CMP8-HEA3 (p65/S536E positions in the RelA protein, which correspond to position 846 in HEA3).

[0144] In some alternatives, the HEA3 transcription factor is a CMP8-responsive HEA3 transcription factor. In some alternatives, the CMP8-responsive HEA3 transcription factor comprises at least one point mutation in the p65 domain that enhances transcriptional activity. In some alternatives, the point mutation is at position 310 of the sequence of the RelA protein which corresponds to position 621 of the wild-type HEA3 protein, and the wild-type HEA4 protein. In some alternatives, the amino acid sequence comprises a sequence set forth in SEQ ID NO: 10 (SEQ ID NO: 10; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWMEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGGVEIFDMLLATSSRFRMMNLQGEEFVCL
KSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLAQ
LLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVEE
TDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYETF

QSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFPS
GQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAPK
PTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIPV
APHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADMDF
SALLSQISS). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 10. SEQ ID NO: 10 is the sequence of CMP8-HEA3 containing one point mutation (K310Q positions in the RelA protein) in the p65 domain that enhances transcriptional activity. This is referred to as CMP8-HEA3 (p65/K310Q). Position 310 of the RelA protein is position 621 of wild-type HEA3 and wild-type HEA4.

[0145] In some alternatives, the HEA3 transcription factor is a CMP8-responsive HEA3 transcription factor. In some alternatives, the CMP8-responsive HEA3 transcription factor comprises at least two point mutations in the p65 domain that enhances transcriptional activity. In some alternatives, the point mutations are at positions 621 of the sequence of the wild-type HEA3 (The 310 position in the RelA protein corresponds to position 621 in wild type HEA3). In some alternatives, the amino acid sequence comprises a sequence set forth in SEQ ID NO: 11 (SEQ ID NO: 11;
MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWMEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGGVEIFDMLLATSSRFRMMNLQGEEFVCL
KSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLAQ
LLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVEE
TDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYETF
QSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFPS
GQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAPK
PTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIPV
APHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADMDF

SALLSQISS). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 11. SEQ ID NO: 11 comprises the sequence of CMP8-HEA3 containing two point mutations (K310Q and S536E are positions in the RelA protein, which correspond to positions 621 (K310A of the RelA protein) and 846 (S536E of the RelA protein) in both HEA3 and HEA4) in the p65 domain that enhance transcriptional activity. This is referred to as CMP8-HEA3 (p65/S536E/K310Q positions in the RelA protein, which correspond to position 621 and 846 in both HEA3 and HEA4.

[0146] In some alternatives, the system employs a synthetic transcriptional activator which, in the presence of the drug, binds a synthetic promoter upstream of a transgene to induce expression. In some alternatives, the transcriptional activator is HEA4. HEA4 comprises an estrogen receptor ligand binding domain ((ER-LBD) and a p65 domain. In some alternatives, the HEA4 further comprises an HNF1alpha DNA binding domain. In some alternatives, the HEA4 comprises at last three point mutations in the ER-LBD that ablate binding to endogenous estrogen, and confer higher sensitivity to 4-hydroxytamoxifen, fulvestrant, and estrogen analogs compared to wild-type HEA3. In some alternatives, the positions of the three point mutations are at positions 400, 543 and 544 in HEA4 transcription factor. In some alternatives, the amino acid sequence of the HEA4 comprising the at least three mutations comprise an amino acid sequence set forth in SEQ ID NO: 4 (SEQ ID NO: 4;

MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPVKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKGMEHLYSMKCKNVVPLYDLLLEAADAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FKSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP

SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADM
DFSALLSQISS). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 4. SEQ ID NO: 4 comprises the sequence of wild-type HEA4 containing three point mutations (G400V, M543A, L544A) in the ER-LBD that ablate binding to endogenous estrogen, and confer higher sensitivity to 4-hydroxytamoxifen, fulvestrant, and estrogen analogs compared to wild-type HEA3.

[0147] In some alternatives, the HEA4 transcription factor comprises at least one point mutation. In some alternatives, the at least one mutation is in the p65 domain and enhances transcriptional activity. In some alternatives, the at least one mutation is at position 846 of the wild type HEA4 transcription factor. In some alternatives, the amino acid sequence of the HEA4 comprising the at least one mutation comprises an amino acid sequence set forth in SEQ ID NO: 5 (SEQ ID NO: 5; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPVKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKGMEHLYSMKCKNVVPLYDLLLEAADAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FKSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM
DFSALLSQISS). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 5. SEQ ID NO: 5 comprises the sequence of HEA4

containing one point mutation (S536E positions in the RelA protein) in the p65 domain that enhances transcriptional activity. This is referred to as HEA4 (p65/S536E). The mutation S536E refers to the mutation at position 536 of WT RelA. This position translates to position 846 of HEA3. The mutation K310Q refers to the mutation at position 310 of WT RelA. This position translates to position 621 of HEA3.

[0148] In some alternatives, the HEA4 transcription factor comprises at least one point mutation. In some alternatives, the at least one mutation is in the p65 domain and enhances transcriptional activity. In some alternatives, the at least one mutation is at position 621 of the HEA4 transcription factor. In some alternatives, the amino acid sequence of the HEA4 comprising the at least one mutation comprises an amino acid sequence set forth in SEQ ID NO: 6 (SEQ ID NO: 6; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPVKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKGMEHLYSMKCKNVVPLYDLLLEAADAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADM DFSALLSQISS). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 6. SEQ ID NO: 6 comprises the sequence of HEA4 containing one point mutation (K310Q positions in the RelA protein) in the p65 domain that enhances transcriptional activity. This is referred to as HEA4 (p65/K310Q). K310Q refers to the position in RelA, which corresponds to position 621 in WT HEA4.

[0149] In some alternatives, the HEA4 transcription factor comprises at least two point mutations. In some alternatives, the at least two mutations are in the p65 domain and enhances transcriptional activity. In some alternatives, at least two mutations are at positions 846 and 621 of the HEA4 transcription factor. In some alternatives, the amino acid sequence of the HEA4 comprising the at least two mutations comprise an amino acid sequence set forth in SEQ ID NO: 7 (SEQ ID NO: 7; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPVKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKGMEHLYSMKCKNVVPLYDLLLEAADAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM DFSALLSQISS). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 7. SEQ ID NO: 7 comprises the sequence of HEA4 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA4 (p65/S536E/K310Q positions in the RelA protein). K310Q in RelA corresponds to position 621 in HEA4; S536E corresponds to position 846 in HEA4.

[0150] Additional chimeric transcription factors are also contemplated herein. In some alternatives, the HEA4 transcription factor comprises HNF1alpha, an ER-LBD that is the same as HEA4, and a VP64 activation domain instead of the p65 activation domain nucleotide sequence (referred herein as HEA4(VP64), and is encoded by SEQ ID NO: 24

(atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg
cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct
ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc
atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc
tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac
cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg
aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac
caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc
agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag
ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct
gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc
ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagc
gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc
ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc
atggaacaccccgtgaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga
tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct
gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga
tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc
ctgagccacatccggcacatgagcaacaagggaatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct
gctgctcgaggctgccgatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca
cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt
ggacgctctggacgacttcgaccttgacatgttgggttccgacgcgctggatgattttgatttggacatgctgggaagcgacgcactgg
atgactttgatctcgatatgctcggctctgacgcattggacgacttcgacttggatatgctgggttct; HEA4 (VP64)). In some alternatives, HEA4(VP64) comprises an amino acid sequence set forth in SEQ ID NO: 25

(MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF

SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPVKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKGMEHLYSMKCKNVVPLYDLLLEAADAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVDALDDFDLDMLGSDALDDFDLD
MLGSDALDDFDLDMLGSDALDDFDLDMLGS). Some alternatives include a nucleic acid sequence that encodes the amino acid sequence set forth in SEQ ID NO: 25. In some alternatives herein, the chimeric transcription factor is HEA4(VP64), and is encoded by SEQ ID NO: 24. In some alternatives, HEA4(VP64) comprises an amino acid sequence set forth in SEQ ID NO: 25.

[0151] In some alternatives, HEA4 comprises HNF1alpha, an ER-LBD that is the same as HEA4, and an HSF1 activation domain instead of a p65 activation domain. HEA4 (HSF-1) comprises HNF1alpha, ER-LBD that is the same as HEA4, and HSF1 activation domain instead of a p65 activation domain, and is encoded by SEQ ID NO: 26 (atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg
cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct
ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc
atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc
tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac
cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg
aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac
caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc
agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag
ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct
gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc
ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccctatcctgtacagcgagtacgaccccaccagacccttcagc
gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc
ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc
atggaacaccccgtgaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga
tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct
gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga

tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc ctgagccacatccggcacatgagcaacaagggaatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct gctgctcgaggctgccgatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt ggaaaagtgcctcagcgtagcctgcctggacaagaatgagctcagtgaccacttggatgctatggactccaacctggataacctgca gaccatgctgagcagccacggcttcagcgtggacaccagtgccctgctggacctgttcagcccctcggtgaccgtgcccgacatga gcctgcctgaccttgacagcagcctggccagtatccaagagctcctgtctccccaggagcccccaggcctcccgaggcagagaac agcagcccggattcagggaagcagctggtgcactacacagcgcagccgctgttcctgctggaccccggctccgtggacaccggga gcaacgacctgccggtgctgtttgagctgggagagggctcctacttctccgaaggggacggcttcgccgaggaccccaccatctcc ctgctgacaggctcggagcctcccaaagccaaggaccccactgtctcc). In some alternatives, herein the chimeric transcription factor is HEA4(HSF-1) and is encoded by SEQ ID NO: 26. In some alternatives, herein the chimeric transcription factor is HEA4(HSF-1) and comprises an amino acid sequence set forth in SEQ ID NO: 27 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPVKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKGMEHLYSMKCKNVVPLYDLLLEAADAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEKCLSVACLDKNELSDHLDAMDS NLDNLQTMLSSHGFSVDTSALLDLFSPSVTVPDMSLPDLDSSLASIQELLSPQEPPRPP EAENSSPDSGKQLVHYTAQPLFLLDPGSVDTGSNDLPVLFELGEGSYFSEGDGFAEDP TISLLTGSEPPKAKDPTVS). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 27.

[0152] In some alternatives herein the chimeric transcription factor is HEA4(Arnt). HEA4(Arnt) comprises HNF1alpha, ER-LBD that is the same as HEA4, and an Arnt activation domain instead of an p65 activation domain amino acid sequence. In some

alternatives, HEA4(Arnt) is encoded by a sequence set forth in SEQ ID NO: 28 (atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccctatcctgtacagcgagtacgaccccaccagacccttcagc gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc atggaacaccccgtgaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc ctgagccacatccggcacatgagcaacaagggaatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct gctgctcgaggctgccgatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt gcctgaggtcttccaggagatgctgtccatgctgggagatcagagcaacagctacaacaatgaagaattccctgatctaactatgtttc ccccctttcagaa). In some alternatives, HEA4(Arnt) comprises an amino acid sequence set forth in SEQ ID NO: 29 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF

SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPVKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKGMEHLYSMKCKNVVPLYDLLLEAADAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVPEVFQEMLSMLGDQSNSYNNEEF
PDLTMFPPFSE). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 29.

[0153] "Selectable marker cassette," has its plain and ordinary meaning when read in light of the specification, and may be used, for example, to describe a gene that encodes a “selectable marker” and is introduced into a vector or a cell that confers a trait for artificial selection. A selectable marker cassette can be a screenable marker to allow a researcher to distinguish between wanted and unwanted cells, or to enrich for a specific cell type. In some alternatives, a gene delivery polynucleotide is provided. In some alternatives, the gene delivery polynucleotide comprises a selectable marker cassette. The selectable marker cassette as described herein, encodes a protein (the selectable marker) that is used for selecting or tracking a protein or cell that has a protein of interest. In the alternatives described herein, the fusion protein provided herein can comprise a marker sequence that can be selected in experiments, such as flow cytometry. In some alternatives, the marker is the protein Her2tG.

[0154] In some alternatives, the selectable marker is encoded by an EGFRt nucleotide sequence, wherein the selectable maker is encoded by a sequence set forth in SEQ ID NO: 30 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacgcaaagtgtgtaacggaataggt
attggtgaatttaaagactcactctccataaatgctacgaatattaaacacttcaaaaactgcacctccatcagtggcgatctccacatcct
gccggtggcatttaggggtgactccttcacacatactcctcctctggatccacaggaactggatattctgaaaaccgtaaaggaaatca
cagggtttttgctgattcaggcttggcctgaaaacaggacggacctccatgcctttgagaacctagaaatcatacgcggcaggaccaa
gcaacatggtcagttttctcttgcagtcgtcagcctgaacataacatccttgggattacgctccctcaaggagataagtgatggagatgt
gataatttcaggaaacaaaaatttgtgctatgcaaatacaataaactggaaaaaactgtttgggacctccggtcagaaaaccaaaattat
aagcaacagaggtgaaaacagctgcaaggccacaggccaggtctgccatgccttgtgctcccccgagggctgctggggcccgga
gcccagggactgcgtctcttgccggaatgtcagccgaggcagggaatgcgtggacaagtgcaaccttctggagggtgagccaagg
gagtttgtggagaactctgagtgcatacagtgccacccagagtgcctgcctcaggccatgaacatcacctgcacaggacggggacc

agacaactgtatccagtgtgcccactacattgacggcccccactgcgtcaagacctgcccggcaggagtcatgggagaaaacaaca ccctggtctggaagtacgcagacgccggccatgtgtgccacctgtgccatccaaactgcacctacggatgcactgggccaggtcttg aaggctgtccaacgaatgggcctaagatcccgtccatcgccactgggatggtgggggccctcctcttgctgctggtggtggccctgg ggatcggcctcttcatgtga). In some alternatives, the selectable marker comprises an EGFRt amino acid sequence set forth in SEQ ID NO: 31 (MLLLVTSLLLCELPHPAFLLIPRKVCNGIGIGEFKDSLSINATNIKHFKNCTSISGDLHI LPVAFRGDSFTHTPPLDPQELDILKTVKEITGFLLIQAWPENRTDLHAFENLEIIRGRT KQHGQFSLAVVSLNITSLGLRSLKEISDGDVIISGNKNLCYANTINWKKLFGTSGQKT KIISNRGENSCKATGQVCHALCSPEGCWGPEPRDCVSCRNVSRGRECVDKCNLLEGE PREFVENSECIQCHPECLPQAMNITCTGRGPDNCIQCAHYIDGPHCVKTCPAGVMGE NNTLVWKYADAGHVCHLCHPNCTYGCTGPGLEGCPTNGPKIPSIATGMVGALLLLL VVALGIGLFM). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 31.

[0155] In some alternatives, the selectable marker is encoded by a Her2t nucleotide sequence, set forth in SEQ ID NO: 32 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccatgccaccctgagtgtcagcccca gaatggctcagtgacctgttttggaccggaggctgaccagtgtgtggcctgtgcccactataaggaccctcccttctgcgtggcccgct gccccagcggtgtgaaacctgacctctcctacatgcccatctggaagtttccagatgaggagggcgcatgccagccttgccccatca actgcacccactcctgtgtggacctggatgacaagggctgccccgccgagcagagagccagccctctgacgtccatcatctctgcg gtggttggcattctgctggtcgtggtcttgggggtggtctttgggatcctcatctga). In some alternatives, the selectable marker comprises the Her2t amino acid sequence set forth in SEQ ID NO: 33 (MLLLVTSLLLCELPHPAFLLIPCHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCV ARCPSGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTSII SAVVGILLVVVLGVVFGILI). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 33.

[0156] In some alternatives, the selectable marker is encoded by theHer2tG nucleotide sequence set forth in SEQ ID NO: 34 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccatgccaccctgagtgtcagccccag aatggctcagtgacctgttttggaccggaggctgaccagtgtgtggcctgtgcccactataaggaccctcccttctgcgtggcccgctg ccccagcggtgtgaaacctgacctctcctacatgcccatctggaagtttccagatgaggagggcgcatgccagccttgccccatcaa ctgcacccactcctgtgtggacctggatgacaagggctgccccgccgagcagagagccagcccgttaacgggtggaggcagcgg

aggtggctccatcatctctgcggtggttggcattctgctggtcgtggtcttgggggtggtctttgggatcctcatctga). In some alternatives, the selectable marker comprises the Her2tG amino acid sequence, set forth in SEQ ID NO: 35 (MLLLVTSLLLCELPHPAFLLIPCHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCV ARCPSGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTGG GSGGGSIISAVVGILLVVVLGVVFGILI). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 35.

[0157] In some alternatives, the selectable marker is encoded by the CD19t nucleotide sequence, set forth in SEQ ID NO: 36 (atgccacctcctcgcctcctcttcttcctcctcttcctcacccccatggaagtcaggcccgaggaacctctagtggtgaaggtggaag agggagataacgctgtgctgcagtgcctcaaggggacctcagatggccccactcagcagctgacctggtctcgggagtccccgctt aaacccttcttaaaactcagcctggggctgccaggcctgggaatccacatgaggcccctggccatctggcttttcatcttcaacgtctct caacagatgggggcttctacctgtgccagccggggcccccctctgagaaggcctggcagcctggctggacagtcaatgtggagg gcagcggggagctgttccggtggaatgtttcggacctaggtggcctgggctgtggcctgaagaacaggtcctcagagggccccagc tcccttccgggaagctcatgagccccaagctgtatgtgtgggccaaagaccgccctgagatctgggagggagagcctccgtgtgtc ccaccgagggacagcctgaaccagagcctcagccaggacctcaccatggcccctggctccacactctggctgtcctgtggggtacc ccctgactctgtgtccaggggccccctctcctggacccatgtgcaccccaaggggcctaagtcattgctgagcctagagctgaagga cgatcgcccggccagagatatgtgggtaatggagacgggtctgttgttgccccgggccacagctcaagacgctggaaagtattattgt caccgtggcaacctgaccatgtcattccacctggagatcactgctcggccagtactatggcactggctgctgaggactggtggctgga aggtctcagctgtgactttggcttatctgatcttctgcctgtgttcccttgtgggcattcttcatcttcaaagagccctggtcctgaggagga aaagataa). In some alternatives, the selectable marker comprises the CD19t amino acid sequence, set forth in SEQ ID NO: 37 (MPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLKGTSDGPTQQLTWSRESP LKPFLKLSLGLPGLGIHMRPLAIWLFIFNVSQQMGGFYLCQPGPPSEKAWQPGWTVN VEGSGELFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRPEIWEGE PPCVPPRDSLNQSLSQDLTMAPGSTLWLSCGVPPDSVSRGPLSWTHVHPKGPKSLLS LELKDDRPARDMWVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITARPVLWH WLLRTGGWKVSAVTLAYLIFCLCSLVGILHLQRALVLRRKR). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 37.

[0158] In some alternatives, the selectable marker is encoded by the DHFRdm nucleotide sequence set forth in SEQ ID NO: 38

(atggttggttcgctaaactgcatcgtcgctgtgtcccagaacatgggcatcggcaagaacggggacttcccctggccaccgctcag gaatgaatccagatatttccagagaatgaccacaacctcttcagtagaaggtaaacagaatctggtgattatgggtaagaagacctggt tctccattcctgagaagaatcgacctttaaagggtagaattaatttagttctcagcagagaactcaaggaacctccacaaggagctcattt tctttccagaagtctagatgatgccttaaaacttactgaacaaccagaattagcaaataaagtagacatggtctggatagttggtggcagt tctgtttataaggaagccatgaatcacccaggccatcttaaactatttgtgacaaggatcatgcaagactttgaaagtgacacgttttttcc agaaattgatttggagaaatataaacttctgccagaatacccaggtgttctctctgatgtccaggaggagaaaggcattaagtacaaattt gaagtatatgagaagaatgat). In some alternatives, the selectable marker comprises the DHFRdm amino acid sequence, set forth in SEQ ID NO: 39 (VGSLNCIVAVSQNMGIGKNGDFPWPPLRNESRYFQRMTTTSSVEGKQNLVIMGKKT WFSIPEKNRPLKGRINLVLSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLEKYKLLPEYPGVLSDVQE EKGIKYKFEVYEKND). Some alternatives include a nucleic acid comprising a nucleic acid sequence that encodes SEQ ID NO: 39.

[0159] In some alternatives, a system for inducible expression of a chimeric antigen receptor is provided, wherein the system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor comprising a ligand binding domain specific for a ligand selected from a tumor specific molecule, viral specific molecule, or any other selected molecule expressed on a target cell population, wherein the ligand can elicit recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is preferably optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide coding for an intracellular signaling domain; and b) a second nucleic acid comprising a second promoter operably linked to nucleic acid coding for the first promoter inducible by drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives, the drug is tamoxifen and/or its metabolites. In some alternatives, the second promoter is constitutive or inducible. In some alternatives, the first promoter comprises a nucleic acid sequence of SEQ ID NO: 23 (SEQ ID NO: 23;

tagttaataatctacaatagttaataatctacaatagttaataatctacaatagttaataatctacaatagttaataatctacaatagttaataat ctacaatagttaataatctacaagagctcagggtatataatg). In some alternatives, the second promoter is a constitutive promoter. In some alternatives, the second promoter is the EF1αp. In some alternatives, the transcriptional activator comprises an amino acid sequence set forth in SEQ ID NO's: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11. In some alternatives, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives, both vectors are packaged in a viral vector. In some alternatives, the viral vector is a lentivirus. In some alternatives, the first and second nucleic acid comprise a vector. In some alternatives, the first nucleic acid further comprises a nucleic acid sequence coding for a selectable marker. In some alternatives, the second nucleic acid further comprises a nucleic acid coding for a selectable marker. In some alternatives, a system for inducible expression is provided, wherein the system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor. In some alternatives, the transcriptional activator is HEA3 or HEA4. In some alternatives, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises mutations that allow selective binding to the drug ligand. In some alternatives, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some

alternatives, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least three mutations that allow selective binding to the drug ligand, wherein HEA4 comprises an estrogen receptor ligand binding domain. In some alternatives, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to the drug ligand. Mutations in the ER-LBD affect drug to receptor binding. In some alternatives, the HEA3 further comprises an HNF1alpha DNA binding domain. In some alternatives, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand, wherein HEA4 comprises an estrogen receptor ligand binding domain, wherein the estrogen receptor ligand binding domain comprises mutations that allow selective binding to the drug ligand. In some alternatives, the HEA4 further comprises an HNF1alpha DNA binding domain. In some alternatives, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives, HEA4 comprises three mutations in the ER-LBD that enhance sensitivity to drug compared to HEA3. In some alternatives, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives, the variant of a wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives, the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID No: 1 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK

LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FKSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADM
DFSALLSQISS). SEQ ID NO: 1 comprises one point mutation in the ER-LBD that ablates binding to endogenous estrogen, but confers nanomolar specificity to 4-OHT, fulvestrant and other estrogen analogs. In some alternatives, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID No: 2 (SEQ ID NO: 2; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FKSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM
DFSALLSQISS). SEQ ID NO: 2 comprises a point mutation in HEA3, in the p65 domain which enhances transcriptional activity and is referred to as HEA3 (p65/S536E positions in

the RelA protein). In some alternatives, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID NO: 3 (SEQ ID NO: 3; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADM DFSALLSQISS). SEQ ID NO: 3 comprises a sequence of HEA3 containing one point mutation (K310Q positions in the RelA protein) in the p65 domain that enhances transcriptional activity. This is referred to as HEA3(p65/K310Q). In some alternatives, the variant of the wild type HEA3 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives, the variant of the wild type HEA4 transcription factor is encoded by at least one or more nucleic acid sequences set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID NO: 8 (SEQ ID NO: 8; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR

KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWMEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGGVEIFDMLLATSSRFRMMNLQGEEFVCL
KSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLAQ
LLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVEE
TDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYETF
KSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFPS
GQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAPK
PTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIPV
APHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADMDF
SALLSQISS). SEQ ID NO: 8 comprises the sequence of HEA3 containing three point mutations (L384M, M421G, G521R) in the ER-LBD that ablate binding to endogenous estrogen, and confer nanomolar sensitivity to CMP8 and 4-hydroxytamoxifen. This is referred to as CMP8-HEA3.In some alternatives, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID NO: 9 (SEQ ID NO: 9;

MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWMEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGGVEIFDMLLATSSRFRMMNLQGEEFVCL
KSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLAQ
LLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVEE
TDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYETF
KSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFPS
GQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAPK

PTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIPV APHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADMDF SALLSQISS). SEQ ID NO: 9 is the sequence of CMP8-HEA3 containing one point mutation (S536E positions in the RelA protein) in the p65 domain that enhances transcriptional activity. This is referred to as CMP8-HEA3(p65/S536E positions in the RelA protein). In some alternatives, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID NO: 10 (SEQ ID NO: 10; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWMEILMIGLV WRSMEHPGKLLFAPNLLLDRNQGKCVEGGVEIFDMLLATSSRFRMMNLQGEEFVCL KSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLAQ LLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVEE TDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYETF QSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFPS GQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAPK PTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIPV APHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADMDF SALLSQISS). SEQ ID NO: 10 is the sequence of CMP8-HEA3 containing one point mutation (K310Q positions in the RelA protein) in the p65 domain that enhances transcriptional activity. This is referred to as CMP8-HEA3(p65/K310Q positions in the RelA protein). In some alternatives, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID NO: 11 (SEQ ID NO: 11; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP

SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWMEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGGVEIFDMLLATSSRFRMMNLQGEEFVCL
KSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLAQ
LLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVEE
TDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYETF
QSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFPS
GQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAPK
PTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIPV
APHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADMDF
SALLSQISS). SEQ ID NO: 11 comprises the sequence of CMP8-HEA3 containing two point mutations (K310Q and S536E positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as CMP8-HEA3(p65/S536E/K310Q positions in the RelA protein). In some alternatives, the polypeptide that modulates checkpoint signaling inhibits negative checkpoint regulators. In some alternatives, the negative checkpoint regulator comprises PD-1, VISTA, LAG-3 and/or TIM3. In some alternatives, the second promoter is constitutive or inducible. In some alternatives, the second nucleic acid further comprises a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized, a polynucleotide coding for a transmembrane domain and a polynucleotide encoding an intracellular signaling domain. In some alternatives, the first promoter is in opposite orientation to the second promoter. In some alternatives, the ligand binding domain is an antibody fragment, preferably a binding fragment thereof. In some alternatives, the ligand binding domain is a single chain variable fragment. In some alternatives, the tumor specific molecule is CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, or MAGE A3 TCR or combinations thereof. In some alternatives, the system employs a synthetic transcriptional activator which, in the presence of a drug binds a synthetic promoter

upstream of a transgene to induce expression. In some alternatives, the transcriptional activator is HEA3. In some alternatives, the drug is tamoxifen. In some alternatives, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein.

[0160] Additional changes can be made to the transcriptional activator to increase the properties of the transcription factor including, without limitation, altering one or more amino acids in the estrogen receptor ligand binding domain and/or altering one or more amino acids in the p65 transactivating domain. Altering amino acids in the estrogen receptor binding domain can provide for more specific and higher sensitivity binding of the drug to the transcriptional activator. In some alternatives, HEA4 comprises at least three point mutations. For example, mutations can be made at amino acid position 400, 543, and 544. In some alternatives, the wild type HEA4 comprises the sequence set forth in SEQ ID NO: 4 (SEQ ID NO: 4; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPVKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKGMEHLYSMKCKNVVPLYDLLLEAADAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FKSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADM DFSALLSQISS). SEQ ID NO: 4 comprises the sequence of wild-type HEA4 containing three point mutations (G400V, M543A, L544A) in the ER-LBD that ablate binding to

endogenous estrogen, and confer higher sensitivity to 4-hydroxytamoxifen, fulvestrant, and estrogen analogs compared to wild-type HEA3. The transcriptional activator with altered sequence has increased affinity for tamoxifen or 4-hydroxytamoxifen, fulvestrant, and estrogen analogs compared to wild-type HEA3. Altering amino acids in the p65 transactivating domain can provide for increased expression of the transgene in the absence of activation of the transduced cells (SEQ ID NO: 5 and SEQ ID NO: 6).

[0161] In the absence of tamoxifen, TamR-tf is excluded from the nucleus by binding of cytosolic heat-shock protein 90 (HSP90) to the tamoxifen binding active site and transgene expression is in the "OFF" state. Nanomolar concentrations of cytosolic tamoxifen actively outcompete HSP90 for ER-LBD binding, resulting in TamR-tf translocation to the nucleus. Upon nuclear translocation, TamR-tf is readily available to bind its restricted synthetic promoter. In the presence of tamoxifen, binding of TamR-tf to 7xHBD/mE1B promoter induces the "ON" state of transgene expression. In some alternatives, this transcriptional regulator can be modified to provide for varying level of control of transgene expression. Amino acid substitutions in the LBD of TamR-tf (HEA3) permit selective responsiveness to tamoxifen and its metabolites, where 4-hydroxy tamoxifen (4-OHT) is the most pharmacologically active metabolite, with respect to TamR-tf (HEA3) activity, while lacking interaction with endogenous estrogen.

[0162] In some alternatives, a system for inducible expression of a transgene is provided. In some alternatives, the transgene encodes a chimeric antigen receptor. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, is provided. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, is provided, the system comprises: a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from a tumor specific molecule, a viral specific molecule, or other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b)

a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives, the transcriptional activator is HEA3 or HEA4. In some alternatives, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective and high sensitivity binding to the drug ligand. In some alternatives, the HEA3 further comprises an HNF1alpha DNA binding domain. Mutations in the ER-LBD affect drug-to-receptor binding. In some alternatives, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective and high sensitivity binding to the drug ligand. In some alternatives, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives, the HEA4 further comprises an HNF1alpha DNA binding domain. In some alternatives, HEA4 comprises three mutations in the ER-LBD that enhance sensitivity to drug compared to HEA3. Mutations in the ER-LBD affect drug-to-receptor binding. In some alternatives, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives, the variant of the wild type HEA3 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives, the HEA3 transcription factor is encoded by a nucleic acid sequence set forth in

SEQ ID NO: 12 (SEQ ID NO: 12;
atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcaggc
actcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagctg
gccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccccat
cctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccctg
gcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaacca
gagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcggaa
gcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccacca
agaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaaccccag
caaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcaggg
cctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagctgt
ctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagcct
gaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagcg
aggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggctt
cgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagcat
ggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggagatc
ttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcctgc
tgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaagatca
ccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatcctg
agccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacctgct
gctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctcacct
ggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgtgga
gttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattcaagagcatcatg
aagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagcgtgc
ccaagcctgcccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttccccagcg
gccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccatggt
gtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacctacc
caggccggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaatagca
ccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcccca
cacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccagcac
cagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttctccagcattgccgacatggacttcagcg

ccctgctgtcccagatcagcagc). In some alternatives, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 13 (SEQ ID NO: 13;

atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcaggc
actcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagctg
gccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccccat
cctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccctg
gcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaacca
gagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcggaa
gcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccacca
agaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaaccccag
caaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcaggg
cctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagctgt
ctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagcct
gaccgccgatcagatggtgtccgctctgctggacgccgagcccctatcctgtacagcgagtacgaccccaccagacccttcagcg
aggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggctt
cgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagcat
ggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggagatc
ttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcctgc
tgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaagatca
ccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatcctg
agccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacctgct
gctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctcacct
ggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgtgga
gttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattcaagagcatcatg
aagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagcgtgc
ccaagcctgcccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttccccagcg
gccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccatggt
gtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacctacc
caggccgggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaatagca
ccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcccca

cacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccagcac cagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttcagcg ccctgctgtcccagatcagcagc). In some alternatives, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 14 (SEQ ID NO: 14;

atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcaggc actcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagctg gccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacggcgaggacttcacccccccccat cctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccctg gcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaacca gagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcggaa gcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccacca agaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaaccccag caaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcaggg cctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagctgt ctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagcct gaccgccgatcagatggtgtccgctctgctggacgccgagcccctatcctgtacagcgagtacgaccccaccagacccttcagcg aggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggctt cgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagcat ggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggagatc ttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcctgc tgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaagatca ccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatcctg agccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacctgct gctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctcacct ggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgtgga gttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcatcatg aagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagcgtgc ccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttccccagcg gccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccatggt gtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacctacc

caggccggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaatagca
ccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcccca
cacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccagcac
cagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttctccagcattgccgacatggacttcagcg
ccctgctgtcccagatcagcagc). In some alternatives, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 19 (SEQ ID NO: 19;
atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcaggc
actcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagctg
gccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacggcgaggacttcacccccccccat
cctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccctg
gcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaacca
gagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcggaa
gcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccacca
agaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaaccccag
caaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcaggg
cctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagctgt
ctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagcct
gaccgccgatcagatggtgtccgctctgctggacgccgagcccctatcctgtacagcgagtacgaccccaccagacccttcagcg
aggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggctt
cgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggatggaaatcctgatgatcggcctcgtgtggagaagcat
ggaacaccccggcaagctgctgttcgccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcggcgtggagat
cttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcctg
ctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaagatc
accgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatcct
gagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacctg
ctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctcac
ctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgtg
gagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattcaagagcatc
atgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagcgt
gcccaagcctgcccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttccccag

cggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccatg gtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggccctcctgcccctaaaccta cccaggccggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaatag caccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgccc cacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccagc accagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttctccagcattgccgacatggacttcag cgccctgctgtcccagatcagcagc). In some alternatives, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 20 (SEQ ID NO: 20; atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcaggc actcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagctg gccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccccat cctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccctg gcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaacca gagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcggaa gcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccacca agaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaaccccag caaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcaggg cctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagctgt ctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagcct gaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagcg aggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggctt cgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggatggaaatcctgatgatcggcctcgtgtggagaagcat ggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcggcgtggagat cttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcctg ctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaagatc accgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatcct gagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacctg ctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctcac ctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgtg gagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattcaagagcatc

atgaagaagtccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagcgt
gcccaagcctgccccccagccctacccttttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttccccag
cggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccatg
gtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgccccctaaaccta
cccaggccggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaatag
caccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgccc
cacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccagc
accagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttcag
cgccctgctgtcccagatcagcagc). In some alternatives, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 21 (SEQ ID NO: 21;
atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcaggc
actcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagctg
gccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccccat
cctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccctg
gcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaacca
gagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcggaa
gcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccacca
agaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaaccccag
caaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcaggg
cctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagctgt
ctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagcct
gaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagcg
aggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggctt
cgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggatggaaatcctgatgatcggcctcgtgtggagaagcat
ggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcggcgtggagat
cttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcctg
ctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaagatc
accgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatcct
gagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacctg
ctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctcac

ctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgtg
gagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcatc
atgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagcgt
gcccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttccccag
cggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccatg
gtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaaccta
cccaggccggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaatag
caccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgccc
cacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccagc
accagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttctccagcattgccgacatggacttcag
cgccctgctgtcccagatcagcagc). In some alternatives, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 22 (SEQ ID NO: 22;
atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcaggc
actcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagctg
gccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccccat
cctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccctg
gcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaacca
gagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcggaa
gcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccacca
agaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaaccccag
caaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcaggg
cctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagctgt
ctgctggcgatatgagagccgccaacctgtggcccagcccccctgatgatcaagcggagcaagaagaacagcctggccctgagcct
gaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagcg
aggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggctt
cgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggatggaaatcctgatgatcggcctcgtgtggagaagcat
ggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcggcgtggagat
cttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcctg
ctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaagatc
accgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatcct

gagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacctg
ctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctcac
ctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgtg
gagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcatc
atgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagcgt
gcccaagcctgcccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttccccag
cggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccatg
gtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaaccta
cccaggccggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaatag
caccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgccc
cacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccagc
accagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttcag
cgccctgctgtcccagatcagcagc). In some alternatives, the variant of a wild type HEA4 transcription factor comprises at least one or more amino acid sequences set forth in SEQ ID Nos: 4-7. In some alternatives, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15 (SEQ ID NO: 15; atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcaggc
actcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagctg
gccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccccat
cctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccctg
gcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaacca
gagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcggaa
gcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccacca
agaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaaccccag
caaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcaggg
cctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagctgt
ctgctggcgatatgagagccgccaacctgtggcccagcccccctgatgatcaagcggagcaagaagaacagcctggccctgagcct
gaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagcg
aggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggctt
cgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagcat
ggaacaccccgtgaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggagatc

ttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcctgc
tgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaagatca
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cagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttcagcg
ccctgctgtcccagatcagcagc). In some alternatives, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8.

[0163] In some alternatives, the inducible promoter functions in a lentiviral construct and/or in lymphocytes.

Chimeric Antigen Receptors.

[0164] A system with an enhanced sensitivity to a drug ligand for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, comprises: a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from a tumor specific molecule, a viral specific

molecule, or any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In other alternatives, another polynucleotide coding for a chimeric antigen receptor is under the control of a constitutive promoter. In some alternatives, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8.

Ligand binding domain.

[0165] In some alternatives, the chimeric receptor nucleic acid comprises a polynucleotide coding for a ligand binding domain. In some alternatives, the ligand binding domain specifically binds to a tumor a viral molecule, or other molecule expressed on a target or selected cell population, and it may be humanized. In some alternatives, a ligand binding domain, includes without limitation, receptors or portions thereof, small peptides, peptidomimetics, substrates, cytokines, and the like. In some alternatives, the ligand binding domain is an antibody or fragment thereof, preferably a binding fragment thereof, any of which may be humanized. A nucleic acid sequence coding for an antibody or antibody fragment can readily be determined. In a specific alternative, the polynucleotide codes for a scFv that specifically binds CD19. In other specific alternatives, the polynucleotide codes for a single chain Fv that specifically binds HER2, CE7, hB7H3, or EGFR and, optionally, said polynucleotide encodes a humanized version thereof. The sequences of these antibodies and binding domains thereof are known to or can readily be determined by those of skill in the art. In some alternatives, the polynucleotide codes for a single scFv that specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC or VAR2CSA.

[0166] Tumor antigens are proteins that are produced by tumor cells that elicit an immune response. The selection of the ligand binding domain of the invention will depend on the type of cancer to be treated, and can target tumor antigens or other tumor cell surface molecules. A tumor sample from a subject can be characterized for the presence of certain biomarkers or cell surface markers. For example, breast cancer cells from a subject can be positive or negative for each of Her2Neu, Estrogen receptor, and/or the Progesterone receptor. A tumor antigen or cell surface molecule that is found on the individual subject's tumor cells is selected. Tumor antigens and cell surface molecules are well known in the art and include, for example, carcinoembryonic antigen (CEA), prostate specific antigen, PSMA, Her2/neu, estrogen receptor, progesterone receptor, ephrinB2, CD19, CD20, CD22, CD23, CD123, CS-1, CE7, hB7H3, ROR1, mesothelin, c-Met, GD-2, and/or MAGE A3 TCR. In some alternatives, the tumor antigen or tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR and/or any combinations thereof. In some alternatives, a target molecule is a cell surface molecule that is found on tumor cells and is not substantially found on normal tissues, or restricted in its expression to non-vital normal tissues.

[0167] In some alternatives, the target is CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, GD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC, and/or VAR2CSA.

[0168] In one alternative, the target molecule on the tumor comprises one or more epitopes associated with a malignant tumor. Malignant tumors express a number of proteins that can serve as target antigens for T cell receptor or chimeric receptor mediated recognition. Other target molecules belong to the group of cell transformation-related molecules such as the oncogene HER-2/Neu/ErbB2. In some alternatives, the tumor antigen is selectively expressed or overexpressed on the tumor cells as compared to control cells of the same tissue type. In other alternatives, the tumor antigen is a cell surface polypeptide.

[0169] Once a tumor cell surface molecule that may be targeted with a chimeric receptor is identified, an epitope of the target molecule is selected and characterized. Antibodies that specifically bind a tumor cell surface molecule can be prepared using methods of obtaining monoclonal antibodies, methods of phage display, methods to generate

human or humanized antibodies, or methods using a transgenic animal or plant engineered to produce human antibodies. Phage display libraries of partially or fully synthetic antibodies are available and can be screened for an antibody or fragment thereof that can bind to the target molecule. Phage display libraries of human antibodies are also available. In some alternatives, antibodies specifically bind to a tumor cell surface molecule and do not cross react with nonspecific components such as bovine serum albumin or other unrelated antigens. Once identified, the amino acid sequence or polynucleotide sequence coding for the antibody can be isolated and/or determined.

[0170] Antibodies or antigen binding fragments include all or a portion of polyclonal antibodies, a monoclonal antibody, a human antibody, a humanized antibody, a synthetic antibody, a chimeric antibody, a bispecific antibody, a minibody, and a linear antibody. “Antibody fragments" has its plain and ordinary meaning when read in light of the specification, and may be used, for example, to described a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody and can readily be prepared. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments. In some alternatives, the antibody fragments are Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; or multispecific antibodies formed from antibody fragments. Any of such aforementioned antibodies or antibody fragments can be humanized and used with the compositions and methods described herein.

[0171] In some alternatives, a number of different antibodies that bind to a particular tumor cell surface molecule can be isolated and characterized. In some alternatives, the antibodies are characterized based on epitope specificity of the targeted molecule. In addition, in some cases, antibodies that bind to the same epitope can be selected based on the affinity of the antibody for that epitope. In some alternatives, an antibody has an affinity of at least 1 mM, and preferably <50 nM. In some alternatives, the antibody has an affinity of 50 nM, 100 nM, 200 nM, 300nM 400 nM, 500 nM, 1uM, 100uM, 200uM, 300uM, 400uM, 500uM, 600uM, 700 uM, 800uM, 900uM or 1mM or an affinity within a range defined by any two of the aforementioned values. In some alternatives, an antibody is selected that has a higher affinity for the epitope, as compared to other antibodies. For

example, an antibody is selected that has at least a 2 fold, at least a 5 fold, at least a 10 fold, at least a 20 fold, at least a 30 fold, at least a 40 fold, or at least a 50 fold greater affinity than a reference antibody that binds to the same epitope or an affinity that is greater than a reference antibody within a range defined by any two of the aforementioned values.

[0172] In some alternatives, target molecules are CD19, CD20, CD22, CD23, CE7, hB7H3, EGFR, CD123, CS-1, ROR1, mesothelin, Her2, c-Met, PSMA, GD-2, or MAGE A3 TCR or any combination thereof. In some alternatives, the antibody or binding fragment there of specific for these target molecules is humanized.

[0173] In specific alternatives, the target antigen is CD19, CD20, CD22, EGFRvIII, EphA2, IL13Ra2, oaGD2, GD2, CD33, Mesothelin, ROR-1, and/orVAR2CSA. A number of antibodies specific for CD19, CD20, CD22, EGFRvIII, EphA2, IL13Ra2, oaGD2, GD2, CD33, Mesothelin, ROR-1 and/or VAR2CSA are known to those of skill in the art and can be readily characterized for sequence, epitope binding, and affinity. The disclosure also contemplates variable regions that have at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity to that of the scFv for CD19, CD20, CD22, EGFRvIII, EphA2, IL13Ra2, oaGD2, GD2, CD33, Mesothelin, ROR-1 and/orVAR2CSA.

[0174] "Humanized antibodies," has its plain and ordinary meaning when read in light of the specification, and may be used, for example, and may refer to antibodies from non-human species whose protein sequences have been modified to increase their similarity to antibody variants produced naturally in humans. The process of "humanization" can be applied to monoclonal antibodies developed for administration to humans (for example, antibodies developed as anti-cancer drugs). Humanization can be desirable when the process of developing a specific antibody involves utilization of a non-human immune system (such as that in mice). The protein sequences of antibodies produced in this way are partially distinct from homologous antibodies occurring naturally in humans, and are therefore potentially immunogenic when administered to human patients. Humanized antibodies are distinct from chimeric antibodies, in that they have the protein sequences made more similar to human antibodies but can carry a larger stretch of non-human protein. A derivative of a humanized antibody can refer to a segment of an antibody or sequence that is derived from a humanized antibody. In some alternatives, the ligand binding domain comprises a humanized

antibody or portion thereof. In some alternatives, the ligand binding domain comprises a scFv. In some alternatives, the scFv is a humanized scFv.

[0175] In some alternatives, the scFv binds specifically to CD19, CD22, CD20, B7H3 receptor, L1CAM, EGFR, EGFRVIII, EphA2, FITC(E2), GD2, Her2, IL13R2a (hu08) VlVh, IL13Ra2, IL13Ra2, oaGD2, ROR1, CD33, Mesothelin, and/or VAR2CSA.

[0176] Humanization can be desirable in some alternatives for reducing the immunogenicity of monoclonal antibodies that are derived from xenogeneic sources, such as, for example, rodents. Humanization is also desirable in some alternatives so as to improve the interaction of the antibody or a fragment thereof with the human immune system. Due to the development of hybridoma technology, a large number of xenogeneic antibodies are highly immunogenic in humans, which can ultimately limit their clinical applications especially when administration may need to be repeated. Additionally, they can be rapidly removed from the circulation and can cause systemic inflammatory effects as well. Therefore, humanization strategies are desirable in some alternatives to circumvent these situations. Techniques for antibody humanization are known to those skilled in the art.

[0177] In some alternatives, a polynucleotide coding for a ligand binding domain is operably linked to a polynucleotide coding for a spacer region. In some alternatives, the polynucleotide coding for a ligand binding domain can also have one or more restriction enzyme sites at the 5' and/or 3' ends of the coding sequence in order to provide for easy excision and replacement of the polynucleotide with another polynucleotide coding for a ligand binding domain coding for a different antigen or that has different binding characteristics. For example, a restriction site, NheI, is encoded upstream of the leader sequence; and a 3' RsrII located within the hinge region allows subcloning of any desirable scFv into a chimeric receptor vector. In some alternatives, the polynucleotide is codon optimized for expression in mammalian cells, such as humans. Subcloning into a restriction site of a desired vector is a technique that is appreciated by those skilled in the art.

[0178] In some alternatives, the polynucleotide coding for a ligand binding domain is operably linked to a signal peptide. In some alternatives, the signal peptide is a signal peptide for granulocyte colony stimulating factor. Polynucleotides coding for other signal peptides such as CD8 alpha can be utilized. In some alternatives, the polynucleotide codes for CD8 alpha.

[0179] In some alternatives, the polynucleotide coding for a ligand binding domain is operably linked to a promoter. A promoter is selected that provides for expression of the chimeric antigen receptor in a mammalian cell, such as a human cell. In a specific alternative, the promoter is an inducible promoter.

Spacer

[0180] In some alternatives, the chimeric receptor nucleic acid comprises a polynucleotide coding for a spacer region. Typically, a spacer region is found between the ligand binding domain and the transmembrane domain of the chimeric receptor. In some alternatives, a spacer region provides for flexibility of the ligand binding domain and allows for high expression levels in lymphocytes. For example, a CD19-specific chimeric receptor having a spacer domain of 229 amino acids had less antitumor activity than a CD19-specific chimeric receptor with a short spacer region comprised of the modified IgG4 hinge only. In some alternatives, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor.

[0181] In some alternatives, a spacer region has at least 10 to 229 amino acids, 10 to 200 amino acids, 10 to 175 amino acids, 10 to 150 amino acids, 10 to 125 amino acids, 10 to 100 amino acids, 10 to 75 amino acids, 10 to 50 amino acids, 10 to 40 amino acids, 10 to 30 amino acids, 10 to 20 amino acids, or 10 to 15 amino acids, or a length within a range defined by any two of the aforementioned lengths. In some alternatives, a spacer region has 12 amino acids or less, 119 amino acids or less, or 229 amino acids or less but greater than 1 or 2 amino acids. In some alternatives, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor.

[0182] In some alternatives, the spacer region is derived from a hinge region of an immunoglobulin molecule. In some alternatives, a spacer region comprises all or a portion of the hinge region from a human IgG1, human IgG2, a human IgG3, or a human IgG4, and can contain one or more amino acid substitutions. In some alternatives, a portion of the hinge region includes the upper hinge amino acids found between the variable heavy chain and the core, and the core hinge amino acids including a polyproline region. In some alternatives, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor.

[0183] In some alternatives, a short spacer region has 12 amino acids or less and comprises all or a portion of a IgG4 hinge region sequence or variant thereof, an intermediate spacer region has 119 amino acids or less and comprises all or a portion of a IgG4 hinge region sequence and a CH3 region or variant thereof, and a long spacer has 229 amino acids or less but not zero and comprises all or a portion of a IgG4 hinge region sequence, a CH2 region, and a CH3 region or variant thereof. In some alternatives, a short spacer region has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 amino acids or a size within a range defined by any two of the aforementioned amino acid lengths. In some alternatives, a medium spacer region has 13, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 or 119 amino acids or a size within a range defined by any two of the aforementioned amino acid lengths. In some alternatives, a spacer region has 120, 130, 140, 150, 160, 170, 180, 190, 200, 210 or 219 amino acids or a size within a range defined by any two of the aforementioned amino acid lengths.

[0184] A polynucleotide coding for a spacer region can be readily prepared by synthetic or recombinant methods from the amino acid sequence. In some alternatives, a polynucleotide coding for a spacer region is operably linked to a polynucleotide coding for a transmembrane region. In some alternatives, the polynucleotide coding for the spacer region can also have one or more restriction enzyme sites at the 5' and/or 3' ends of the coding sequence in order to provide for easy excision and replacement of the polynucleotide with another polynucleotide coding for a different spacer region. In some alternatives, the polynucleotide coding for the spacer region is codon optimized for expression in mammalian cells, such as human cells.

[0185] In an alternative, the spacer region is a hinge region sequence from IgG1, IgG2, IgG3, or IgG4 or a portion thereof, a hinge region sequence from IgG1, IgG2, IgG3, or IgG4 in combination with all or a portion of a CH2 region or variant thereof, a hinge region sequence from IgG1, IgG2, IgG3, or IgG4 in combination with all or a portion of a CH3 region or variant thereof, and a hinge region sequence from IgG1, IgG2, IgG3, or IgG4 in combination with all or a portion of a CH2 region or variant thereof, and/or a CH3 region or variant thereof. In some alternatives, a short spacer region is a modified IgG4 hinge sequence having 12 amino acids or less but greater than one or two amino acids, an intermediate sequence is a IgG4 hinge sequence with a CH3 sequence having 119 amino acids or less but

greater than one or two amino acids; or a IgG4 hinge sequence with a CH2 and CH3 region having 229 amino acids or less but greater than one or two amino acids.

Transmembrane domain.

[0186] In some alternatives, the chimeric receptor nucleic acid comprises a polynucleotide coding for a transmembrane domain. The transmembrane domain provides for anchoring of the chimeric receptor in the membrane.

[0187] In an alternative, the transmembrane domain that naturally is associated with one of the domains in the chimeric receptor is used. In some cases, the transmembrane domain can be selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins to minimize interactions with other members of the receptor complex.

[0188] The transmembrane domain can be derived either from a natural or a synthetic source. When the source is natural, the domain can be derived from any membrane-bound or transmembrane protein.

[0189] Transmembrane regions in some alternatives comprise at least the transmembrane region(s) of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3, CD45, CD4, CD8, CD9, CD16, CD22; CD33, CD37, CD64, CD80, CD86, CD134, CD137 and/or CD154.

[0190] A transmembrane domain can be synthetic or a variant of a naturally occurring transmembrane domain. In some alternatives, synthetic or variant transmembrane domains comprise predominantly hydrophobic residues such as leucine and valine, for example. In some alternatives, a transmembrane domain can have at least 80%, 85%, 90%, 95%, or 100% amino acid sequence identity with a transmembrane domain as set forth in SEQ ID NO: 110-113 or an amino acid sequence identity that is within a range defined by any two of the aforementioned values. Variant transmembrane domains preferably have a hydrophobic score of at least 50 as calculated by Kyte Doolittle.

[0191] A polynucleotide coding for a transmembrane domain can be readily prepared by synthetic or recombinant methods. In some alternatives, a polynucleotide coding for a transmembrane domain is operably linked to a polynucleotide coding for an intracellular signaling region. In some alternatives, the polynucleotide coding for a

transmembrane domain can also have one or more restriction enzyme sites at the 5' and/or 3' ends of the coding sequence in order to provide for easy excision and replacement of the polynucleotide coding for a transmembrane domain with another polynucleotide coding for a different transmembrane domain. In some alternatives, the polynucleotide coding for a transmembrane domain is codon optimized for expression in mammalian cells, such as human cells.

Intracellular signaling domain.

[0192] In some alternatives, the chimeric receptor nucleic acid comprises a polynucleotide coding for an intracellular signaling domain. The intracellular signaling domain provides for activation of one function of the transduced cell expressing the chimeric receptor upon binding to the ligand expressed on tumor cells. In some alternatives, the intracellular signaling domain contains one or more intracellular signaling domains. In some alternatives, the intracellular signaling domain is a portion of and/or a variant of an intracellular signaling domain that provides for activation of at least one function of the transduced cell.

[0193] Examples of intracellular signaling domains for use in a chimeric receptor of the disclosure include the cytoplasmic sequences of the CD3 zeta chain, and/or co-receptors that act in concert to initiate signal transduction following chimeric receptor engagement, as well as any derivative or variant of these sequences and any synthetic sequence that has the same functional capability. T cell activation can be said to be mediated by two distinct classes of cytoplasmic signaling sequence: those that initiate antigen-dependent primary activation and provide a T cell receptor like signal (primary cytoplasmic signaling sequences) and those that act in an antigen-independent manner to provide a secondary or co-stimulatory signal (secondary cytoplasmic signaling sequences). Primary cytoplasmic signaling sequences that act in a stimulatory manner can contain signaling motifs, which are known as receptor tyrosine-based activation motifs or ITAMs. Examples of ITAM containing primary cytoplasmic signaling sequences suitable for use with alternatives described herein include those derived from CD3 zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and/or CD66d.

[0194] In a preferred alternative, the intracellular signaling domain of the chimeric receptor can be designed to comprise the CD3-zeta signaling domain by itself or

combined with any other desired cytoplasmic domain(s). For example, the intracellular signaling domain of the chimeric receptor can comprise a CD3zeta chain and a costimulatory signaling region.

[0195] The costimulatory signaling region refers to a portion of the chimeric receptor comprising the intracellular domain of a costimulatory molecule. A costimulatory molecule is a cell surface molecule other than an antigen receptor or their ligands that is required for a response of lymphocytes to an antigen. Examples of such molecules suitable for use in the alternatives described herein include CD27, CD28, 4-1BB (CD 137), OX40, CD30, CD40, lymphocyte function-associated antigen-1 (LFA-l), CD2, CD7, LIGHT, NKG2C, B7-H3, zeta chain associated protein kinase (ZAP70), and/or a ligand that specifically binds with CD83.

[0196] The intracellular signaling sequences of the chimeric receptor can be linked to each other in a random or specified order. In some alternatives, a short oligo- or polypeptide linker, preferably between 2 and 10 amino acids in length, such as 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids in length, can form the linkage. In one alternative, the intracellular signaling domains comprises all or a portion of the signaling domain of CD3-zeta or variant thereof and all or a portion of the signaling domain of CD28 or a variant thereof. In another alternative, the intracellular signaling domain comprises all or a portion of the signaling domain of CD3-zeta or variant thereof and all or a portion of the signaling domain of 4-lBB or variant thereof. In yet another alternative, the intracellular signaling domain comprises all or a portion of the signaling domain of CD3-zeta or variant thereof, all or a portion of the signaling domain of CD28 or variant thereof, and all or a portion of the signaling domain of 4-lBB or variant thereof. In a specific alternative, the amino acid sequence of the intracellular signaling domain comprises a variant of CD3zeta and a portion of the 4-1BB intracellular signaling domain.

[0197] In an alternative, a polynucleotide coding for an intracellular signaling domain comprises a 4-1BB intracellular domain linked to a portion of a CD3zeta domain. In other alternatives, a 4-1BB intracellular domain and a CD28 intracellular domain are linked to a portion of a CD3 zeta domain.

[0198] In some alternatives, the intracellular domain is encoded by a sequence set forth in SEQ ID NO: 114. In some alternatives, the intracellular domain is encoded by a

sequence set forth in SEQ ID NO: 116. In some alternatives, the intracellular domain is encoded by a sequence set forth in SEQ ID NO: 118. In some alternatives, the intracellular domain comprises an amino acid sequence set forth in SEQ ID NO: 115. In some alternatives, the intracellular domain comprises an amino acid sequence set forth in SEQ ID NO: 117. In some alternatives, the intracellular domain comprises an amino acid sequence set forth in SEQ ID NO: 119.

[0199] A polynucleotide coding for an intracellular signaling domain can be readily prepared by synthetic or recombinant methods from the amino acid sequence. In some alternatives, the polynucleotide coding for an intracellular signaling domain can also have one or more restriction enzyme sites at the 5' and/or 3' ends of the coding sequence in order to provide for easy excision and replacement of the polynucleotide coding for an intracellular signaling domain with another polynucleotide coding for a different intracellular signaling domain. In some alternatives, the polynucleotide coding for an intracellular signaling domain is codon optimized for expression in mammalian cells. In some alternatives, the mammalian cells are human cells.

Marker sequences.

[0200] In some alternatives, the system further comprises one or more marker sequences under the control of an inducible promoter. A marker sequence can provide for selection of transduced cells, and/or identification of transduced cells. In some alternatives, the marker sequence is for a selection of transduced cells and/or identification of transduced cells. In some alternatives, the marker sequence is operably linked to a polynucleotide sequence coding for a linker sequence. In some alternatives, the linker sequence is a cleavable linker sequence. In some alternatives, the linker is 2A linker such as, for example, T2A, P2A or F2A. In some alternatives, the linker is a cleavable T2A linker.

[0201] A number of different marker sequences can be employed. Typically, a marker sequence has a functional characteristic that allows for selection of transduced cells and/or detection of transduced cells. In some alternatives, the marker sequence is compatible with transduction of human lymphocytes. In some alternatives, the marker sequence allows for selection of transduced cells and/or detection of transduced cells.

[0202] The positive selectable marker can be a gene, which upon being introduced into the host cell, expresses a dominant phenotype permitting positive selection of

cells carrying the gene. Genes of this type are known in the art, and include, inter alia, hygromycin-B phosphotransferase gene (hph) which confers resistance to hygromycin B, the amino glycoside phosphotransferase gene (neo or aph) from Tn5, which codes for resistance to the antibiotic G418, the double mutant of the dihydrofolate reductase (DHFR) gene, which provides resistance to methotrexate, DHFR dm. Transduced cells cultured in the presence of these agents will survive and be selected.

[0203] In an alternative, a first nucleic acid further comprises a polynucleotide coding for a marker sequence. In an alternative, the marker sequence is a truncated epidermal growth factor receptor (EGFRt). In some alternatives, the marker sequence is a truncated Her2 sequence (Her2t). Selectable marker sequences that can be used in the alternatives set forth in this disclosure are provided below.

SELECTABLE MARKER SEQUENCES

EGFRt nucleotide sequence:

Atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacgcaaagtgtgtaacggaataggt
attggtgaatttaaagactcactctccataaatgctacgaatattaaacacttcaaaaactgcacctccatcagtggcgatctccacatcct
gccggtggcatttaggggtgactccttcacacatactcctcctctggatccacaggaactggatattctgaaaaccgtaaaggaaatca
cagggtttttgctgattcaggcttggcctgaaaacaggacggacctccatgcctttgagaacctagaaatcatacgcggcaggaccaa
gcaacatggtcagttttctcttgcagtcgtcagcctgaacataacatccttgggattacgctccctcaaggagataagtgatggagatgt
gataatttcaggaaacaaaaatttgtgctatgcaaatacaataaactggaaaaaactgtttgggacctccggtcagaaaaccaaaattat
aagcaacagaggtgaaaacagctgcaaggccacaggccaggtctgccatgccttgtgctccccgagggctgctggggcccgga
gcccagggactgcgtctcttgccggaatgtcagccgaggcagggaatgcgtggacaagtgcaaccttctggagggtgagccaagg
gagtttgtggagaactctgagtgcatacagtgccacccagagtgcctgcctcaggccatgaacatcacctgcacaggacggggacc
agacaactgtatccagtgtgcccactacattgacggcccccactgcgtcaagacctgcccggcaggagtcatgggagaaaacaaca
ccctggtctggaagtacgcagacgccggccatgtgtgccacctgtgccatccaaactgcacctacggatgcactgggccaggtcttg
aaggctgtccaacgaatgggcctaagatcccgtccatcgccactgggatggtgggggccctcctcttgctgctggtggtggccctgg
gatcggcctcttcatgtga (SEQ ID NO: 30);

EGFRt amino acid sequence:

MLLLVTSLLLCELPHPAFLLIPRKVCNGIGIGEFKDSLSINATNIKHFKNCTSISGDLHIL
PVAFRGDSFTHTPPLDPQELDILKTVKEITGFLLIQAWPENRTDLHAFENLEIIRGRTK
QHGQFSLAVVSLNITSLGLRSLKEISDGDVIISGNKNLCYANTINWKKLFGTSGQKTKI
ISNRGENSCKATGQVCHALCSPEGCWGPEPRDCVSCRNVSRGRECVDKCNLLEGEP
REFVENSECIQCHPECLPQAMNITCTGRGPDNCIQCAHYIDGPHCVKTCPAGVMGEN
NTLVWKYADAGHVCHLCHPNCTYGCTGPGLEGCPTNGPKIPSIATGMVGALLLLLV
VALGIGLFM (SEQ ID NO: 31);

Her2t nucleotide sequence:

Atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccatgccaccctgagtgtcagccccag
aatggctcagtgacctgttttggaccggaggctgaccagtgtgtggcctgtgcccactataaggaccctcccttctgcgtggcccgctg
ccccagcggtgtgaaacctgacctctcctacatgcccatctggaagtttccagatgaggagggcgcatgccagccttgccccatcaa
ctgcacccactcctgtgtggacctggatgacaagggctgccccgccgagcagagagccagccctctgacgtccatcatctctgcggt
ggttggcattctgctggtcgtggtcttgggggtggtctttgggatcctcatctga (SEQ ID NO: 32);

Her2t amino acid sequence:
MLLLVTSLLLCELPHPAFLLIPCHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCVA
RCPSGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTSIIS
AVVGILLVVVLGVVFGILI (SEQ ID NO: 33);
Her2tG nucleotide sequence:
Atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccatgccaccctgagtgtcagccccag
aatggctcagtgacctgttttggaccggaggctgaccagtgtgtggcctgtgcccactataaggaccctcccttctgcgtggcccgctg
ccccagcggtgtgaaacctgacctctcctacatgcccatctggaagtttccagatgaggagggcgcatgccagccttgccccatcaa
ctgcacccactcctgtgtggacctggatgacaagggctgccccgccgagcagagagccagcccgttaacgggtggaggcagcgg
aggtggctccatcatctctgcggtggttggcattctgctggtcgtggtcttgggggtggtctttgggatcctcatctga (SEQ ID
NO: 34);
Her2tG amino acid sequence:
MLLLVTSLLLCELPHPAFLLIPCHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCVA
RCPSGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTGGG
SGGGSIISAVVGILLVVVLGVVFGILI (SEQ ID NO: 35);
CD19t nucleotide sequence:
Atgccacctcctcgcctcctcttcttcctcctcttcctcacccccatggaagtcaggcccgaggaacctctagtggtgaaggtggaaga
gggagataacgctgtgctgcagtgcctcaaggggacctcagatggccccactcagcagctgacctggtctcgggagtccccgctta
aacccttcttaaaactcagcctggggctgccaggcctgggaatccacatgaggcccctggccatctggcttttcatcttcaacgtctctc
aacagatgggggggcttctacctgtgccagccgggggccccctctgagaaggcctggcagcctggctggacagtcaatgtggaggg
cagcggggagctgttccggtggaatgtttcggacctaggtggcctgggctgtggcctgaagaacaggtcctcagagggccccagct
ccccttccgggaagctcatgagccccaagctgtatgtgtgggccaaagaccgccctgagatctgggagggagagcctccgtgtgtc
ccaccgagggacagcctgaaccagagcctcagccaggacctcaccatggcccctggctccacactctggctgtcctgtggggtacc
ccctgactctgtgtccaggggccccctctcctggacccatgtgcaccccaaggggcctaagtcattgctgagcctagagctgaagga
cgatcgcccggccagagatatgtgggtaatggagacgggtctgttgttgccccgggccacagctcaagacgctggaaagtattattgt
caccgtggcaacctgaccatgtcattccacctggagatcactgctcggccagtactatggcactggctgctgaggactggtggctgga
aggtctcagctgtgactttggcttatctgatcttctgcctgtgttcccttgtgggcattcttcatcttcaaagagccctggtcctgaggagga
aaagataa (SEQ ID NO: 36);
CD19t amino acid sequence:
MPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLKGTSDGPTQQLTWSRESP
LKPFLKLSLGLPGLGIHMRPLAIWLFIFNVSQQMGGFYLCQPGPPSEKAWQPGWTVN
VEGSGELFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRPEIWEGE
PPCVPPRDSLNQSLSQDLTMAPGSTLWLSCGVPPDSVSRGPLSWTHVHPKGPKSLLS
LELKDDRPARDMWVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITARPVLWH
WLLRTGGWKVSAVTLAYLIFCLCSLVGILHLQRALVLRRKR (SEQ ID NO: 37)
DHFRdm nucleotide sequence:
Atggttggttcgctaaactgcatcgtcgctgtgtcccagaacatgggcatcggcaagaacggggacttcccctggccaccgctcagg
aatgaatccagatatttccagagaatgaccacaacctcttcagtagaaggtaaacagaatctggtgattatgggtaagaagacctggtt
ctccattcctgagaagaatcgacctttaaagggtagaattaatttagttctcagcagagaactcaaggaacctccacaaggagctcatttt
ctttccagaagtctagatgatgccttaaaacttactgaacaaccagaattagcaaataaagtagacatggtctggatagttggtggcagtt
ctgtttataaggaagccatgaatcacccaggccatcttaaactatttgtgacaaggatcatgcaagactttgaaagtgacacgttttttcca
gaaattgatttggagaaatataaacttctgccagaatacccaggtgttctctctgatgtccaggaggagaaaggcattaagtacaaattt
gaagtatatgagaagaatgat (SEQ ID NO: 38); and
DHFRdm amino acid sequence:
VGSLNCIVAVSQNMGIGKNGDFPWPPLRNESRYFQRMTTTSSVEGKQNLVIMGKKT
WFSIPEKNRPLKGRINLVLSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW

IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLEKYKLLPEYPGVLSDVQE EKGIKYKFEVYEKND (SEQ ID NO: 39).

DNA spacer sequence:

Gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc (SEQ ID NO: 120).

The DNA spacer sequence may be described also as the 7xHBD/mE1B_DNA spacer.

[0204] In some alternatives herein, the DNA spacer, a 46 base pair sequence, may reside in between the 7xHBD/mE1B promoter and inducible transgene. The DNA spacer which comprises SEQ ID NO: 120, allows enhanced gene expression of the transgene. In some alternatives herein, a vector construct comprising a DNA spacer between a promoter and a transgene showed an increase in transcription of the transgene as compared to a vector that had the promoter and the transgene without a DNA spacer. In some alternatives herein, the DNA spacer enhanced transgene expression as compared to a vector that did not have a DNA spacer between the promoter and the transgene. In some alternatives, a DNA spacer is between the mE1B promoter and the transgene.

[0205] In some alternatives, the polynucleotide coding for the marker sequence is operably linked to a polynucleotide coding for a linker sequence. In some alternatives, the linker is a 2A linker, such as, for example, T2A, P2A, E2A or F2A.

[0206] A polynucleotide coding for marker sequence can be readily prepared by synthetic or recombinant methods from the amino acid sequence. In some alternatives, a polynucleotide coding for a marker sequence is operably linked to a polynucleotide coding for an intracellular signaling domain. In some alternatives, the polynucleotide coding for a marker sequence can also have one or more restriction enzyme sites at the 5' and/or 3' ends of the coding sequence in order to provide for easy excision and replacement of the polynucleotide coding for a marker sequence with another polynucleotide coding for a different marker sequence. In some alternatives, the polynucleotide coding for a marker sequence is codon optimized for expression in mammalian cells, preferably humans.

[0207] In some alternatives, two or more marker sequences can be employed. In some alternatives, a first marker sequence is under control of a constitutive promoter and provides for an indication that the transduced cell is expressing the transgene. In other alternatives, a second marker sequence is under the control of the inducible promoter and provides an indication that the transgene expression has been induced. In some alternatives, the marker under the control of the inducible promoter can be used to select for cells in

which noninduced or basal expression is much lower than in other cells by selecting cells that have a lower expression of the marker sequence under the control of the inducible promoter and expand those cells for further applications. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity. In some alternatives, the transgene encodes a protein that modulates T cells. In some alternatives, the transgene encodes a chimeric antigen receptor.

Other Genetic Components under control of Inducible Promoter.

[0208] In some alternatives, the first nucleic acid comprises a polynucleotide sequence coding for genes that promote survival and proliferation, genes that prevent apoptosis, and/or genes that inhibit negative checkpoint signaling under the control of an inducible promoter. Such genes include genes encoding IL-2, IL-7, IL-15, chemokine receptors, Bcl2, CA-Akt, dn-TGFbetaRIII, dn-SHP1/2, PD-1-IFNalpha and/or PD-1CD28 chimeras. These genes are also placed under the control of an inducible promoter as described herein. In some alternatives, the genes encode IL-2, IL-7, IL-15, chemokine receptors, chimeric cytokine receptors, Bcl2, CA-Akt, dn-TGFbetaRII, dn-SHP1/2, PD-1-IFNalpha, and/or PD-1CD28 chimeras. In some alternatives, the gene that modulates checkpoint signaling encodes a polypeptide that inhibits negative checkpoint regulators. In some alternatives, the negative checkpoint regulator comprises PD-1, VISTA, LAG-3 and/or TIM3.

[0209] In some alternatives, a first nucleic acid comprises a first inducible promoter linked to a polynucleotide coding for a cytokine, chemokine receptor, or chimeric cytokine receptor. chemokines, also referred to as chemotactic cytokines, are a group of structurally related proteins that regulate cell trafficking of lymphocytes. In some alternatives, the chemokines are homeostatic or inflammatory. Chemokine receptors include CCR2, CCR7, or CCR15. Cytokines include interleukins such as IL2, IL-12, IL-7, and/or Il-15, interferons, such as interferon δ, tumor necrosis factor, and a TLR4 agonist. Chimeric cytokine receptors can also include CCR(CD122). In some alternatives, the chemokine receptors comprise CCR2, CCR7, and/or CCR15. In some alternatives, the chemokine receptors include CCR2, CCR7, or CCR15. In some alternatives, the cytokines include

interleukins, wherein the interleukins are IL2, IL-12, IL-7 and/or Il-15 or interferons, wherein the interferons comprise interferon δ, tumor necrosis factor, or a TLR4 agonist.

[0210] In some alternatives, a first nucleic acid comprises a first inducible promoter linked to a polynucleotide coding for a polypeptide that regulates apoptosis. In some alternatives, genes that inhibit apoptosis include, for example, Bcl2, and/or CA-Akt. In some alternatives, the polypeptide is Bcl2 or CA-Akt. In some alternatives, genes that inhibit apoptosis include, for example, Survivin, Bcl2, CA-Akt, and/or dnCaspase3. In some alternatives, the polypeptide is Survivin, Bcl2, or CA-Akt and/or dnCaspase 3. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK ETNNKKKEFEETVKKVRRAIEQLAAMD).

[0211] In some alternatives, a first nucleic acid comprises a first inducible promoter linked to a polynucleotide coding for a polypeptide that modulates checkpoint signaling. Such genes include dn-TGFbetaRII, dn-SHP1/2, PD-1-IFNalpha, and/or PD-1CD28 chimeras. In some alternatives, the polypeptide is dn-TGFbetaRII, dn-SHP1/2, PD-1-IFNalpha, and/or PD-1CD28 chimeras. In some alternatives, the polypeptide that modulates checkpoint signaling inhibits negative checkpoint regulators. In some alternatives, the negative checkpoint regulator comprises PD-1, VISTA, LAG-3 and/or TIM3.

[0212] Any number of nucleic acids can be placed under the control of an inducible promoter including those coding for chimeric antigen receptor, a marker sequences, a cytokine, a chemokine, an inhibitor of apoptosis, and/ or an inhibitor of negative checkpoint signaling. In some alternatives, one or more inducible promoters can be utilized to provide for an adequate expression level of each of the nucleic acids. In some alternatives, constructs can be prepared with a gene such as a cytokine under the control of an inducible

promoter and a construct comprising a chimeric antigen receptor under the control of a constitutive promoter. Such constructs are useful to provide for cell survival and proliferation of transduced cells, for example lymphocytes expressing a chimeric antigen receptor.

[0213] In the systems provided herein, the systems are inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor.

[0214] In some alternatives, HEA3 comprises two amino acid mutations, wherein the sequence is encoded by a sequence set forth in SEQ ID NO: 122 (atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacggcgaggacttcacccccccc atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagc gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc atggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc ctgagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct gctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt ggagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcat catgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagc

gtgcccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttcccca gcggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccat ggtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacct acccaggccggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaata gcaccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcc ccacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccag caccagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttca gcgccctgctgtcccagatcagcagc). In some alternatives, the HEA3 comprises an amino acid sequence set forth in SEQ ID NO: 121 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM DFSALLSQISS). This sequence comprises the sequence of HEA3 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA3(p65/S536E/K310Q). K310Q in RelA corresponds to position 621 in HEA3; S536E corresponds to position 846 in HEA3.

Constitutive Promoter Systems.

[0215] In other alternatives, a system comprises a second nucleic acid that comprises a constitutive promoter or a second inducible promoter linked to a transcriptional

activator. In other alternatives, a system comprises a second nucleic acid that comprises a promoter linked to a transcriptional activator. In some alternatives, the promoter is a constitutive promoter or an inducible promoter. In some alternatives, a constitutive promoter includes EF1α promoter, actin promoter, the myosin promoter, the hemoglobin promoter, and the creatine kinase promoter. In some alternatives, viral promoters such as the CMV promoter are excluded. In some alternatives, the constitutive promoter can be linked to one or more of a polynucleotide coding for marker, or a chimeric antigen receptor as described herein.

Constitutive Promoters.

[0216] A constitutive promoter provides for continuous gene expression of the gene under the control of the promoter. In some alternatives, the constitutive promoter is a promoter that provides for gene expression in a lentiviral construct and/or in lymphocytes. In some alternatives, the promoter is not derived from a xenogenic source such as a plant or a virus.

[0217] In a specific alternative, the constitutive promoter comprises EF1α promoter, actin promoter, the myosin promoter, the hemoglobin promoter, and/or the creatine kinase promoter. In some alternatives, viral promoters such as the CMV promoter are excluded.

Transcriptional Activators.

[0218] In some alternatives, the constitutive promoter is operably linked to a transcriptional activator. In some alternatives, the transcriptional activator activates an inducible promoter in the presence of the inducer (e.g. drug).

[0219] In some alternatives, an inducible promoter is induced in the presence of a transcriptional activator. In some alternatives, the transcriptional activator preferentially binds to the promoter in the presence of the drug. In some alternatives, the transcriptional activator is TamR-tf (HEA3 or HEA4). Modification of the transcriptional activator can be made in the amino acid sequence that can affect the ability of an activator to bind to the drug, the promoter, or both. For example, binding in the ER ligand binding domain would affect the binding of the drug to the transcriptional activator. In some alternatives, HEA3 comprises two amino acid mutations, wherein the sequence is encoded by a sequence set forth in SEQ ID NO: 122

(atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg
cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct
ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc
atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc
tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac
cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg
aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac
caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc
agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag
ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct
gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc
ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagc
gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc
ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc
atggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga
tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct
gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga
tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc
ctgagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct
gctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca
cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt
ggagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcat
catgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagc
gtgcccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttcccca
gcggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccat
ggtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacct
acccaggccgggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaata
gcaccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcc
ccacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccag
caccagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttca
gcgccctgctgtcccagatcagcagc). In some alternatives, the HEA3 comprises an amino acid

sequence set forth in SEQ ID NO: 121 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM DFSALLSQISS). This sequence comprises the sequence of HEA3 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA3(p65/S536E/K310Q). K310Q in RelA corresponds to position 621 in HEA3; S536E corresponds to position 846 in HEA3.

[0220] In some alternatives, the system employs a synthetic transcriptional activator which, in the presence of the drug (e.g.tamoxifen), binds a synthetic promoter upstream of a transgene to induce expression. In some alternatives, it is a variant of a wild type "TamR-tf" HEA3 transcription factor. In some alternatives, it is a variant of a wild type "TamR-tf" HEA4 transcription factor. An exemplary amino acid sequence is provided in SEQ ID NO: 1 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK

LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FKSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADM
DFSALLSQISS). The mutant tamoxifen-specific ligand binding domain of the estrogen receptor ligand binding domain (ER-LBD) is found at amino acids 282-595 of the HEA3 and has a mutation at position 521 (SEQ ID NO: 1; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FKSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADM
DFSALLSQISS). The p65 activation domain of NF-κB (p65 or TAD) is found at amino acids 596 to 862. SEQ ID NO: 1 comprises one point mutation in the ER-LBD that ablates binding to endogenous estrogen, but confers nanomolar specificity to 4-OHT, fulvestrant and

other estrogen analogs. In some alternatives, HEA3 comprises two amino acid mutations, wherein the sequence is encoded by a sequence set forth in SEQ ID NO: 122 (atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagc gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc atggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc ctgagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct gctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt ggagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcat catgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagc gtgcccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttcccca gcggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccat ggtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacct acccaggccgggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaata gcaccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcc ccacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccag

caccagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttca gcgccctgctgtcccagatcagcagc). In some alternatives, the HEA3 comprises an amino acid sequence set forth in SEQ ID NO: 121 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM DFSALLSQISS). This sequence comprises the sequence of HEA3 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA3(p65/S536E/K310Q). K310Q in RelA corresponds to position 621 in HEA3; S536E corresponds to position 846 in HEA3.

[0221] Additional changes can be made to the transcriptional activator to increase the properties of the transcription factor including, without limitation, altering one or more amino acids in the estrogen receptor ligand binding domain and/or altering one or more amino acids in the p65 transactivating domain. Altering amino acids in the estrogen receptor binding domain can provide for more specific and sensitive binding of the drug to the transcriptional activator. For example, mutations are made at amino acid position 400, 543, and 544 of SEQ ID NO: 4 (SEQ ID NO: 4; MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR

VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPVKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKGMEHLYSMKCKNVVPLYDLLLEAADAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FKSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFSSIADM
DFSALLSQISS). SEQ ID NO: 4 comprises the sequence of wild-type HEA4 containing three point mutations (G400V, M543A, L544A) in the ER-LBD that ablate binding to endogenous estrogen, and confer higher sensitivity to 4-hydroxytamoxifen, fulvestrant, and estrogen analogs compared to wild-type HEA3. The transcriptional activator with altered sequence has increased affinity for tamoxifen or 4-OHT. Altering amino acids in the p65 transactivating domain can provide for increased expression of the transgene in the absence of activation of the transduced cells. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity. In some alternatives, the transgene encodes a protein that modulates T cells. In some alternatives, the transgene encodes a chimeric antigen receptor.

Marker

[0222] In some alternatives, the constitutive promoter is operably linked to a polynucleotide coding for a marker polypeptide. Such marker polypeptides are described herein, and include EGFRt, Her2t, and/or DHFRdm.

[0223] In some alternatives, the marker is encoded by a sequence set forth in SEQ ID NO's: 30, 32, 34, 36 or 38. In some alternatives, the marker comprises an amino acid sequence set forth in SEQ ID NO's: 31, 33, 35, 37 or 39.

Chimeric Antigen Receptor

[0224] In some alternatives, the constitutive promoter is operably linked to a polynucleotide coding for a chimeric antigen receptor. In some alternatives, the chimeric antigen receptor comprises a ligand binding domain, wherein the ligand binding domain is specific for a ligand, wherein the ligand is a tumor specific molecule, viral molecule, or any other molecule expressed on a target cell population, wherein the ligand can elicit recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide coding for an intracellular signaling domain. In some alternatives, the spacer is optimized to provide for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor.

Vectors

[0225] A variety of vector combinations can be constructed to provide for efficiency of transduction and transgene expression. In some alternatives, the vector is a dual packaged or single (all in one) viral vector. In other alternatives, the vectors can include a combination of viral vectors and plasmid vectors. Other viral vectors include foamy virus, adenoviral vectors, retroviral vectors, and lentiviral vectors. In some alternatives, the vector is a lentiviral vector. In some alternatives, the vector is a foamy viral vector, adenoviral vectors, retroviral vectors or lentiviral vectors.

[0226] In some alternatives, a plasmid vector or a viral vector comprises a first nucleic acid comprising an inducible promoter linked to a polynucleotide coding for a chimeric antigen receptor. In some alternatives, a plasmid vector or viral vector comprises a first nucleic acid sequence comprising a polynucleotide coding for a gene that enhances cell survival or proliferation, a gene that regulates apoptosis, and/or a gene that modulates checkpoint signaling. In some alternatives, the modulation of checkpoint signaling inhibits negative checkpoint regulators. In some alternatives, the negative checkpoint regulator comprises PD-1, VISTA, LAG-3 and/or TIM3. Such polynucleotides code for a cytokine, a

chimeric cytokine receptor, or a chemokine receptor. In some alternatives, a plasmid vector or a viral vector comprises a first nucleic acid comprising an inducible promoter linked to a polynucleotide coding for a marker sequence. In some alternatives, the marker sequence is compatible with transduction of human lymphocytes. In some alternatives, the marker sequence allows for selection of transduced cells and/or detection of transduced cells. In some alternatives, the marker is a gene that can include inter alia, hygromycin-B phosphotransferase gene (hph), which confers resistance to hygromycin B, the amino glycoside phosphotransferase gene (neo or aph) from Tn5, which codes for resistance to the antibiotic G418, the mutated dihydrofolate reductase (DHFR) gene, which provides resistance to methotrexate, DHFRdm, the pac gene that provides resistance to puromycin, Sh ble gene, which inactivates zeocin, the adenosine deaminase gene (ADA), and/or the multi-drug resistance (MDR) gene. A first nucleic acid can include a number of different polynucleotide sequences all under the control of the inducible promoter. For example, a polynucleotide coding for a chimeric antigenic receptor can be linked to a polynucleotide coding for a marker polypeptide and/or a polynucleotide coding for cytokine or chemokine receptor. In some alternatives, a gene is under the control of the inducible promoter. In some alternatives, the gene encodes a chimeric cytokine receptor.

[0227] In some alternatives, a lentiviral vector comprises a second nucleic acid comprising a constitutive promoter linked to a nucleic acid sequence coding for transcriptional activator that binds to drug and activates expression of an inducible promoter. In some alternatives, a lentiviral vector with a constitutive promoter can also include a nucleic acid sequence including a marker gene, piggybac transposase, and/or a polynucleotide coding for a chimeric antigen receptor. Each element of the nucleic acid can be separated from one another with a sequence such as a T2A self-cleaving sequence. In some alternatives, the elements of the nucleic acid are separated from one another with a sequence self-cleaving sequence. In some alternatives, the self-cleaving sequence is a 2A linker. In some alternatives, the linker is T2A, P2A, E2A or F2A.

[0228] In other alternatives, the heterogeneous (heterogeneous to the vector, e,g, lentiviral vector) nucleic acid sequence is limited by the amount of additional genetic components that can be packaged in the vector. In some alternatives, a construct contains at least two genes heterogenous to the viral vector. In some alternatives, the construct contains

no more than 4 genes heterogenous to the viral vector. The number of genes heterogenous to the viral vector that can be packaged in the vector can be determined by detecting the expression of one or more transgenes, and selecting vector constructs that provide for transduction of at least 10% of the cells and/or detectable expression levels of the transgene in at least 10% of the cells. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity. In some alternatives, the transgene encodes a protein that modulates T cells. In some alternatives, the transgene encodes a chimeric antigen receptor.

[0229] In some alternatives, a lentivirus is a dual packaged virus. A dual packaged virus contains at least one conditional construct comprising an inducible promoter operably linked to a polynucleotide coding for a chimeric antigen receptor. Optionally the conditional construct comprises a marker gene, a nucleic acid for a cytokine, a nucleic acid for a chimeric cytokine receptor, a nucleic acid for a chemokine receptor. In some alternatives, a dual packaged lentivirus contains a constitutive construct comprising a constitutive promoter. In an alternative, the constitutive construct comprises a constitutive promoter linked to a transcriptional activator for the inducible promoter. In some alternatives, the constitutive construct also includes a marker gene and/or a polynucleotide encoding a cytokine or chemokine. In some alternatives of a system with two constructs, each construct can be packaged in a separate viral vector and the viral vectors can be mixed together for transduction in a cell population.

[0230] When the constitutive and conditional constructs both contain a marker gene, the marker gene on each construct is the same or different from one another. In some alternatives, when the constitutive and conditional constructs both contain a polynucleotide coding for a chimeric antigen receptor, the chimeric antigen receptor can be targeted to the same antigen but have different ligand binding domains, can be targeted to the same antigen but different epitopes, or can be targeted to different antigens.

[0231] In some alternatives, the vector is a minicircle. Minicircles are episomal DNA vectors that are produced as circular expression cassettes devoid of any bacterial plasmid DNA backbone. Their smaller molecular size enables more efficient transfections

and offers sustained expression over a period of weeks as compared to standard plasmid vectors that only work for a few days. In some alternatives, a minicircle contains a drug inducible promoter linked to a polynucleotide coding for a chimeric antigen receptor. In some alternatives, the inducible promoter can be linked to chemokine receptor, a marker gene, and/or a cytokine. One or more minicircles can be employed. In some alternatives, a minicircle comprises an inducible promoter linked to a polynucleotide coding for a first chimeric antigen receptor, another minicircle comprises an inducible promoter linked to a polynucleotide coding for a second and different chimeric antigen receptor, and/ or a minicircle comprises an inducible promoter linked to a polynucleotide coding for a chemokine receptor, a chimeric antigen receptor, and a marker gene. Each element of the constructs is separated by a nucleic acid, such as that coding for a self-cleaving T2A sequence. In some alternatives, each element of the constructs is separated by a nucleic acid, such as that coding for a self-cleaving T2A sequence. In some alternatives, each minicircle differs from one another in the chimeric antigen receptor including but not limited to the spacer length and sequence, the intracellular signaling domain, and/or the marker sequence. The minicircle vector can be used with a constitutive lentivirus vector coding for a transcriptional activator for the inducible promoter. In some alternatives, the minicircle vector is used with a constitutive lentivirus vector coding for a transcriptional activator for the inducible promoter. In the systems provided herein, the systems are inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor.

[0232] In some alternatives, the vector is a piggy bac transposon. The PiggyBac (PB) transposon is a mobile genetic element that efficiently transposes between vectors and chromosomes via a "cut and paste" mechanism. During transposition, the PB transposase recognizes transposon-specific inverted terminal repeat sequences (ITRs) located on both ends of the transposon vector and efficiently moves the contents from the original sites and efficiently integrates them into TTAA chromosomal sites. The powerful activity of the PiggyBac transposon system enables genes of interest between the two ITRs in the PB vector to be easily mobilized into target genomes.

[0233] In some alternatives, a PB contains a drug inducible promoter linked to a polynucleotide coding for a chimeric antigen receptor. In some alternatives, the inducible

promoter can be linked to chemokine receptor, a marker gene, and/or a cytokine. One or more PB transposons can be employed. In some alternatives, a PB comprises an inducible promoter linked to a polynucleotide coding for a first chimeric antigen receptor, another PB comprises an inducible promoter linked to a polynucleotide coding for a second and different chimeric antigen receptor, and/ or a PB comprises an inducible promoter linked to a polynucleotide coding for a chemokine receptor, a chimeric antigen receptor, and a marker gene. Each element of the constructs is separated by a nucleic acid, such as that coding for a self-cleaving T2A sequence. In some alternatives, each PB differs from one another in the chimeric antigen receptor including but not limited to the spacer length and sequence, the intracellular signaling domain, and/or the marker sequence. The PB vector can be used with a constitutive lentivirus vector coding for a transcriptional activator for the inducible promoter and constitutive vector comprising the piggyback transposase linked to a constitutive promoter.

[0234] Some alternatives concern a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a polynucleotide coding for chimeric antigen receptor comprising a ligand binding domain, wherein the ligand binding domain is specific for a ligand, wherein the ligand is a tumor specific molecule, viral molecule, or any other molecule expressed on a target cell population, wherein the ligand can elicit recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; and a polynucleotide coding for an intracellular signaling domain; and a second nucleic acid comprising a second constitutive or inducible promoter operably linked to nucleic acid coding for a transcriptional activator for the inducible promoter. In some alternatives, the first and second nucleic acid are in a single lentivirus vector. In some alternatives, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives, the first nucleic acid further comprises a marker gene. In some alternatives, the second nucleic acid further comprises polynucleotide coding for a second and different chimeric antigen receptor. The first and second chimeric antigen receptor can differ from one another in the ligand binding domain, the target antigen, an epitope of the target antigen, the spacer domain in length and sequence (short medium or long), and in the intracellular signaling domains. In some

alternatives, in a single lentivirus construct the first and second nucleic acids can be separated by a genomic insulator nucleic acid such as the sea urchin insulator chromatin domain. In other alternatives, the inducible promoter of the first nucleic acid and the constitutive promoter of the second nucleic acid are in opposite orientation. One or more of these vectors can be used in conjunction with one another to transduce target cells and provide for inducible expression of a chimeric antigen receptor.

Host Cells and Compositions: T lymphocyte populations.

[0235] The compositions described herein provide for genetically modified host cells with the vectors and/or constructs as described herein. In some alternatives, the host cells are CD4+ and/or CD8+ T lymphocytes.

[0236] T lymphocytes can be collected in accordance with known techniques and enriched or depleted by known techniques such as affinity binding to antibodies such as flow cytometry and/or immunomagnetic selection. After enrichment and/or depletion steps, *in vitro* expansion of the desired T lymphocytes can be carried out in accordance with known techniques or variations thereof that will be apparent to those skilled in the art. In some alternatives, the T cells are autologous T cells obtained from the patient.

[0237] For example, the desired T cell population or subpopulation can be expanded by adding an initial T lymphocyte population to a culture medium in vitro, and then adding to the culture medium feeder cells, such as non-dividing peripheral blood mononuclear cells (PBMC), (e.g., such that the resulting population of cells contains at least 5, 10, 20, or 40 or more PBMC feeder cells for each T lymphocyte in the initial population to be expanded); and incubating the culture (e.g. for a time sufficient to expand the numbers of T cells). The non-dividing feeder cells can comprise gamma-irradiated PBMC feeder cells. In some alternatives, the PBMC are irradiated with gamma rays in the range of 3000 to 3600 rads to prevent cell division. In some alternatives, the PBMC are irradiated with gamma rays of 3000, 3100, 3200, 3300, 3400, 3500 or 3600 rads or any value of rads between any two endpoints of any of the listed values to prevent cell division. The order of addition of the T cells and feeder cells to the culture media can be reversed if desired. The culture can typically be incubated under conditions of temperature and the like that are suitable for the growth of T lymphocytes. For the growth of human T lymphocytes, for example, the temperature will generally be at least 25 degrees Celsius, preferably at least 30 degrees, more

preferably 37 degrees. In some alternatives, the temperature for the growth of human T lymphocytes is 22, 24, 26, 28, 30, 32, 34, 36, 37 degrees Celsius or any other temperature between a range defined by any two endpoints of any of the listed values.

[0238] The T lymphocytes expanded include $CD8^+$ cytotoxic T lymphocytes (CTL) and $CD4^+$ helper T lymphocytes that can be specific for an antigen present on a human tumor or a pathogen. In some alternatives, the cells include precursor T cells. In some alternatives, the cells are hematopoietic stem cells.

[0239] In some alternatives, the expansion method can further comprise adding non-dividing EBV-transformed lymphoblastoid cells (LCL) as feeder cells. LCL can be irradiated with gamma rays in the range of 6000 to 10,000 rads. In some alternatives, the LCL are irradiated with gamma rays in of 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500 or 10,000 rads or any amount of rads in between a range defined by any two endpoints of any of the listed values. The LCL feeder cells can be provided in any suitable amount, such as a ratio of LCL feeder cells to initial T lymphocytes of at least 10:1.

[0240] In some alternatives, the expansion method can further comprise adding anti-CD3 and/or anti CD28 antibody to the culture medium (*e.g.*, at a concentration of at least 0.5 ng/ml). In some alternatives, the expansion method can further comprise adding IL-2 and/or IL-7 and/or IL-15 to the culture medium (*e.g.*, wherein the concentration of IL-2 is at least 10 units/ml).

[0241] After isolation of T lymphocytes both cytotoxic and helper T lymphocytes can be sorted into naïve, memory, and effector T cell subpopulations either before or after expansion.

[0242] CD8+ cells can be obtained by using standard methods. In some alternatives, CD8+ cells are further sorted into naïve, central memory, and effector memory cells by identifying cell surface antigens that are associated with each of those types of CD8+ cells. In some alternatives, memory T cells are present in both CD62L+ and CD62L- subsets of CD8+ peripheral blood lymphocytes. PBMC are sorted into CD62L-CD8+ and CD62L+CD8+ fractions after staining with anti-CD8 and anti-CD62L antibodies. In some alternatives, the expression of phenotypic markers of central memory T_{CM} include CD45RO, CD62L, CCR7, CD28, CD3, and/or CD127 and are negative or low for granzyme B. In some alternatives, central memory T cells are CD45RO+, CD62L+, and/or CD8+ T cells. In some

alternatives, effector T_E are negative for CD62L, CCR7, CD28, and/or CD127, and positive for granzyme B and/or perforin. In some alternatives, naïve CD8+ T lymphocytes are characterized by the expression of phenotypic markers of naïve T cells including CD62L, CCR7, CD28, CD3, CD127, and/or CD45RA.

[0243] CD4+ T helper cells are sorted into naïve, central memory, and effector cells by identifying cell populations that have cell surface antigens. CD4+ lymphocytes can be obtained by standard methods. In some alternatives, naïve CD4+ T lymphocytes are CD45RO-, CD45RA+, CD62L+, and/or CD4+ T cells. In some alternatives, central memory CD4+ cells are CD62L+ and/or CD45RO+. In some alternatives, effector CD4+ cells are CD62L- and/or CD45RO-.

[0244] Whether a cell or cell population is positive for a particular cell surface marker can be determined by flow cytometry using staining with a specific antibody for the surface marker and an isotype matched control antibody. A cell population negative for a marker refers to the absence of significant staining of the cell population with the specific antibody above the isotype control, positive refers to uniform staining of the cell population above the isotype control. In some alternatives, a decrease in expression of one or markers refers to loss of 1 log10 in the mean fluorescence intensity and/or decrease of percentage of cells that exhibit the marker of at least 20% of the cells, 25% of-the cells, 30% of the cells, 35% of the cells, 40% of the cells, 45% of the cells, 50% of the cells, 55% of the cells, 60% of the cells, 65% of the cells, 70% of the cells, 75% of the cells, 80% of the cells, 85% of the cells, 90% of the cell, 95% of the cells, and 100% of the cells or any % between 20 and 100% when compared to a reference cell population. In some alternatives, a cell population positive for one or markers refers to a percentage of cells that exhibit the marker of at least 50% of the cells, 55% of the cells, 60% of the cells, 65% of the cells, 70% of the cells, 75% of the cells, 80% of the cells, 85% of the cells, 90% of the cell, 95% of the cells, or 100% of the cells or any % between 50 and 100% when compared to a reference cell population.

[0245] Whether a cell or cell population is positive for a particular cell surface marker can be determined by flow cytometry using staining with a specific antibody for the surface marker and an isotype matched control antibody. A cell population negative for a marker refers to the absence of significant staining of the cell population with the specific antibody above the isotype control, positive refers to uniform staining of the cell population

above the isotype control. In some alternatives, a decrease in expression of one or markers refers to loss of 1 log10 in the mean fluorescence intensity and/or decrease of percentage of cells that exhibit the marker of at least 20% of the cells, 25% of-the cells, 30% of the cells, 35% of the cells, 40% of the cells, 45% of the cells, 50% of the cells, 55% of the cells, 60% of the cells, 65% of the cells, 70% of the cells, 75% of the cells, 80% of the cells, 85% of the cells, 90% of the cell, 95% of the cells, and 100% of the cells or any % between 20 and 100% when compared to a reference cell population. In some alternatives, an increase refers to an increase in mean or median fluorescence intensity and/or to an increase in the number of cells in a cell population that are positive for one or a given marker, such as a population in which s refers to a percentage of cells that exhibit the marker of at least 50% of the cells, 55% of the cells, 60% of the cells, 65% of the cells, 70% of the cells, 75% of the cells, 80% of the cells, 85% of the cells, 90% of the cell, 95% of the cells, or 100% of the cells or any % between 50 and 100% exhibit the marker, e.g., when compared to a reference cell population.

[0246] In some alternatives, populations of CD4+ and CD8+ that are antigen specific can be obtained by stimulating naïve or antigen specific T lymphocytes with antigen. For example, antigen-specific T cell lines or clones can be generated to Cytomegalovirus antigens by isolating T cells from infected subjects and stimulating the cells in vitro with the same antigen. Naïve T cells can also be used. Any number of antigens from tumor cells can be utilized as targets to elicit T cell responses. In some alternatives, the adoptive cellular immunotherapy compositions are useful in the treatment of a disease or disorder including a solid tumor, hematologic malignancy, breast cancer or melanoma.

Modification of T lymphocyte populations.

[0247] In some alternatives, it can be desired to introduce functional genes into the T cells to be used in immunotherapy in accordance with the present disclosure. For example, the introduced gene or genes can improve the efficacy of therapy by promoting the viability and/or function of transferred T cells; or they can provide a genetic marker to permit selection and/or evaluation of *in vivo* survival or migration; or they can incorporate functions that improve the safety of immunotherapy, for example, by making the cell susceptible to controlled expression of the transgene. This can be carried out in accordance with known techniques that will be apparent to those skilled in the art based upon the present disclosure.

[0248] In some alternatives, T cells are modified with a vector coding for drug inducible chimeric receptors as described herein. In some alternatives, the T cells are modified with a vector coding for drug inducible transgenes. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity. In some alternatives, the transgene encodes a protein that modulates T cells. In some alternatives, the transgene encodes a chimeric antigen receptor. In some alternatives, cells are modified with a vector comprising a polynucleotide coding for a chimeric antigen receptor under control of an inducible promoter. In other alternatives, cells are modified with a vector comprising a polynucleotide coding for a cytokine, a chimeric cytokine receptor, chemokine receptor, a gene that regulates apoptosis, or a gene that modulates checkpoint signaling under the control of an inducible promoter. In some alternatives, the T cells are obtained from the subject to be treated, in other alternatives the lymphocytes are obtained from allogeneic human donors, preferably healthy human donors. In some alternatives, the modulation of checkpoint signaling inhibits negative checkpoint regulators. In some alternatives, the negative checkpoint regulator comprises PD-1, VISTA, LAG-3 and/or TIM3.

[0249] Chimeric receptors can be constructed with a specificity for any cell surface marker by utilizing antigen binding fragments or antibody variable domains of, for example, antibody molecules. The antigen binding molecules can be linked to one or more cell signaling modules. In some alternatives, cell signaling modules include CD3 transmembrane domains, CD3 intracellular signaling domains, and/or CD28 transmembrane domains. In some alternatives, the intracellular signaling domain comprises a CD28 transmembrane and signaling domain linked to a CD3 zeta intracellular domain. In some alternatives, a chimeric receptor can also include a transduction marker such as EGFRt.

[0250] In some alternatives, the same or a different chimeric receptor can be introduced into each of population of CD4+ and/or CD8+ T lymphocytes. In some alternatives, the chimeric receptor in each of these populations has a ligand binding domain that specifically binds to the same ligand on the tumor or infected cell or a different antigen or epitope. The cellular signaling modules can differ. In some alternatives, the intracellular

signaling domain of the CD8+ cytotoxic T cells is the same as the intracellular signaling domain of the CD4+ helper T cells. In other alternatives, the intracellular signaling domain of the CD8+ cytotoxic T cells is different than the intracellular signaling domain of the CD4+ helper T cells.

[0251] In some alternatives, each of the CD4 or CD8 T lymphocytes can be sorted into naïve, central memory, effector memory or effector cells prior to transduction, as described herein. In some alternatives, each of the CD4 or CD8 T lymphocytes can be sorted into naïve, central memory, effector memory, or effector cells after transduction.

[0252] As described herein, in some alternatives, naïve CD4+ cells are CD45RO-, CD45RA+, CD62L+, and/or CD4+ positive T cells. In some alternatives, central memory CD4+ cells are CD62L positive and/or CD45RO positive. In some alternatives, effector CD4+ cells are CD62L negative and/or CD45RO positive. Each of these populations can be independently modified with a chimeric receptor.

[0253] As described, in some alternatives, memory T cells are present in both CD62L+ and CD62L- subsets of CD8+ peripheral blood lymphocytes. PBMC are sorted into CD62L-CD8+ and CD62L+CD8+ fractions after staining with anti-CD8 and anti-CD62L antibodies. In some alternatives, the expression of phenotypic markers of central memory T cells (TCM) include CD62L, CCR7, CD28, CD3, and/or CD127 and are negative or low for granzyme B. In some alternatives, central memory T cells are CD45RO+, CD62L+, and/or CD8+ T cells. In some alternatives, effector T cells (T_E) are negative for CD62L, CCR7, CD28, and/or CD127, and positive for granzyme B and/or perforin. In some alternatives, naïve CD8+ T lymphocytes are characterized by CD8+, CD62L+, CD45RO+, CCR7+, CD28+ CD127+, and/or CD45RO+. Each of these populations can be independently modified with a chimeric receptor.

[0254] Various transduction techniques have been developed, which utilize recombinant infectious virus particles for gene delivery. This represents a currently preferred approach to the transduction of T lymphocytes of the present invention. The viral vectors, which have been used in this way include virus vectors derived from simian virus 40, adenoviruses, adeno-associated virus (AAV), lentiviral vectors, and/or retroviruses. Thus, gene transfer and expression methods are numerous but essentially function to introduce and express genetic material in mammalian cells. Several of the above techniques have been used

to transduce hematopoietic or lymphoid cells, including calcium phosphate transfection, protoplast fusion, electroporation, and infection with recombinant adenovirus, adeno-associated virus and retrovirus vectors. Primary T lymphocytes have been successfully transduced by electroporation and by retroviral or lentiviral infection.

[0255] Retroviral and lentiviral vectors provide a highly efficient method for gene transfer into eukaryotic cells. Moreover, retroviral or lentiviral integration takes place in a controlled fashion and results in the stable integration of one or a few copies of the new genetic information per cell.

[0256] It is contemplated that overexpression of a stimulatory factor (for example, a lymphokine or a cytokine) can be toxic to the treated individual. Therefore, it is within the scope of the invention to include gene segments that cause the T cells of the invention to be susceptible to negative selection in vivo. By "negative selection" has its plain and ordinary meaning when read in light of the specification, and may be used, for example, when an infused cell is eliminated as a result of a change in the in vivo condition of the individual. The negative selectable phenotype can result from the insertion of a gene that confers sensitivity to an administered agent, for example, a compound. Negative selectable genes are known in the art, and include, inter alia the following: the Herpes simplex virus type I thymidine kinase (HSV-I TK) gene, which confers ganciclovir sensitivity; the cellular hypoxanthine phosphribosyltransferase (HPRT) gene, the cellular adenine phosphoribosyltransferase (APRT) gene, and bacterial cytosine deaminase.

[0257] In some alternatives, it can be useful to include in the T cells a positive marker that enables the selection of cells of the negative selectable phenotype *in vitro*. The positive selectable marker can be a gene that upon being introduced into the host cell expresses a dominant phenotype permitting positive selection of cells carrying the gene. Genes of this type are known in the art, and include, inter alia, hygromycin-B phosphotransferase gene (hph), which confers resistance to hygromycin B, the amino glycoside phosphotransferase gene (neo or aph) from Tn5, which codes for resistance to the antibiotic G418, the double mutant of the dihydrofolate reductase (DHFRdm) gene, the adenosine deaminase gene (ADA), and/or the multi-drug resistance (MDR) gene.

[0258] A variety of methods can be employed for transducing T lymphocytes, as is well known in the art. In some alternatives, transduction is carried out using lentiviral vectors.

[0259] In some alternatives, CD4+ and CD8+ cells each can separately be modified with an expression vector encoding a chimeric receptor to form defined populations. In some alternatives, cells can be separately modified with a vector comprising a polynucleotide under the control of a constitutive promoter and a vector comprising a polynucleotide coding for a cytokine or chemokine receptor under control of an inducible promoter.

[0260] In some alternatives, these cells are further sorted into subpopulations of naïve, central memory and effector cells as described above, by sorting for cell surface antigens unique to each of those cell populations. In addition, CD4+ or CD8+ cell populations can be selected by their cytokine profile or proliferative activities. For example, CD4+ T lymphocytes that have enhanced production of cytokines such as IL-2, IL-4, IL-10, TNFα, and/or IFNγ, as compared to sham transduced cells or transduced CD8+ cells when stimulated with antigen can be selected. In other alternatives, naïve or central memory CD4+ T cells that have enhanced production of IL-2 and/or TNFα are selected. Likewise, CD8+ cells that have enhanced IFNγ production are selected, as compared to sham transduced CD8+ cells.

[0261] In some alternatives, CD4+ and CD8+ cells are selected that are cytotoxic for antigen bearing cells. In some alternatives, CD4+ are expected to be weakly cytotoxic as compared to CD8+ cells. In a preferred alternative, transduced lymphocytes, such as CD8+ central memory cells, are selected that provide for tumor cell killing in vivo using an animal model established for the particular type of cancer.

[0262] In yet other alternatives, transduced chimeric receptor expressing T cells are selected that can persist *in vivo* using an animal model established for the particular type of cancer. In some alternatives, transduced chimeric receptor CD8+ central memory cells with a short spacer region have been shown to persist *in vivo* after introduction into the animal for 3 days or more, 10 days or more, 20 days or more, 30 days or more, 40 days or more, or 50 days or more.

[0263] The disclosure contemplates that combinations of CD4+ and CD8+ T cells will be utilized in the compositions. In one alternative, combinations of chimeric receptor transduced CD4+ cells can be combined with chimeric receptor transduced CD8+ cells of the same ligand specificity or combined with $CD8^+$ T cells that are specific for a distinct tumor ligand. In other alternatives, chimeric receptor transduced CD8+ cells are combined with chimeric receptor transduced CD4+ cells specific for a different ligand expressed on the tumor. In yet another alternative, chimeric receptor modified CD4+ and CD8+ cells are combined. In some alternatives, CD8+ and CD4+ cells can be combined in different ratios for example, a 1:1 ratio of CD8+ and CD4+, a ratio of 10:1 of CD8+ to CD4+, or a ratio of 100:1 of CD8+ to CD4+, or any other ratio of CD8+ to CD4+ that is between a range defined by any of the listed ratios. In some alternatives, the combined population is tested for cell proliferation in vitro and/or in vivo, and the ratio of cells that provides for proliferation of cells is selected.

[0264] After transduction and/or selection for chimeric receptor bearing cells, the cell populations are preferably expanded in vitro until a sufficient number of cells are obtained to provide for at least one infusion into a human subject, typically around 10^4 cells/kg to 10^9 cells/kg. In some alternatives, the transduced cells are cultured in the presence of antigen bearing cells, anti CD3, anti CD28, and IL 2, IL-7, IL 15, or IL-21 or any combination thereof.

[0265] In some alternatives, CD4+ and CD8+cells that proliferate in response to cytokine stimulation, antigen or tumor targets in vitro or in vivo are selected. For example, CD4+ or CD8+ transduced cells that proliferate vigorously when stimulated with antiCD3 and/ or anti-CD28 are selected. In some alternatives, stimulation of transduced cells provides for enhanced transgene expression in the presence of an inducer (e.g. drug) of those trans genes under the control of an inducible promoter. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity. In some alternatives, the transgene encodes a protein that modulates T cells. In some alternatives, the transgene encodes a chimeric antigen receptor.

[0266] Each of the subpopulations of CD4+ and CD8+ cells can be combined with one another. In a specific alternative, modified naïve or central memory CD4+ cells are combined with modified central memory CD8+ T cells to provide a synergistic cytotoxic effect on antigen bearing cells, such as tumor cells.

Compositions.

[0267] The disclosure provides for an adoptive cellular immunotherapy composition comprising a genetically modified T lymphocyte cell preparation as described herein. In some alternatives, the T lymphocyte cell preparation comprises CD4 + T cells that have a chimeric receptor comprising an extracellular antibody variable domain specific for a ligand associated with the disease or disorder, a spacer region, a transmembrane domain, and an intracellular signaling domain of a T cell receptor or other receptors under the control of a drug inducible promoter as described herein. In other alternatives, an adoptive cellular immunotherapy composition further comprises a chimeric receptor modified tumor-specific CD8+ cytotoxic T lymphocyte cell preparation that provides a cellular immune response, wherein the cytotoxic T lymphocyte cell preparation comprises CD8+ T cells that have a chimeric receptor comprising an extracellular single chain antibody specific for a ligand associated with the disease or disorder, a spacer region, a transmembrane domain, and an intracellular signaling domain of a T cell receptor under the control of a drug inducible promoter as described herein. In some alternatives, the chimeric receptor modified T cell population of the disclosure can persist *in vivo* for at least 3 days or longer. In an alternative, each of these populations can be combined with one another or other cell types to provide a composition. In some alternatives, the T cell population can express genes that modulate the T cell function. In some alternatives, the genes encode cytokines, chemokine receptors and proteins that can modulate T cell function.

[0268] In some alternatives, the CD4+ T helper lymphocyte cell is naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, or bulk CD4+ T cells. In some alternatives, CD4+ helper lymphocyte cell is a naïve CD4+ T cell, wherein the naïve CD4+ T cell comprises a CD45RO-, CD45RA+, and/or is a CD62L+ CD4+ T cell.

[0269] In some alternatives, the CD8+ T cytotoxic lymphocyte cell is a naïve CD8+ T cell, central memory CD8+ T cell, effector memory CD8+ T cell and/or bulk CD8+ T cell. In some alternatives, the CD8+ cytotoxic T lymphocyte cell is a central memory T

cell, wherein the central memory T cell comprises a CD45RO+, CD62L+, and/or CD8+ T cell. In yet other alternatives, the CD8+ cytotoxic T lymphocyte cell is a central memory T cell and the CD4+ helper T lymphocyte cell is a naïve or central memory CD4+ T cell.

[0270] In some alternatives, the compositions comprise T cell precursors. In some alternatives, the compositions comprise hematopoietic stem cells. In some alternatives, the composition comprises a host cell wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells or a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells and a second host cell, wherein the second host cell is a precursor T cell. In some alternatives, the precursor T cell is a hematopoietic stem cell.

Methods

[0271] The disclosure provides methods of making adoptive immunotherapy compositions and uses or methods of using these compositions for performing cellular immunotherapy in a subject having a disease or disorder. In some alternatives, a method of manufacturing the compositions comprises obtaining a modified naïve or central memory CD4+ T helper cell, wherein the modified helper T lymphocyte cell preparation comprises CD4+ T cells that have a chimeric receptor comprising a ligand binding domain specific for a tumor cell surface molecule, a spacer domain, a transmembrane domain, and an intracellular signaling domain under control of an inducible promoter as described herein. In other alternatives, CD4+ cells have a cytokine or chemokine receptor under the control of an inducible promoter. CD4+ cells can also have other genes under control of the inducible promoter (genes that control apoptosis, alter extracellular environment etc).

[0272] In another alternative, a method further comprises obtaining a modified CD8+ central memory T cell, wherein the modified central memory CD8 T lymphocyte cell preparation comprises CD8+ cells that have a chimeric receptor comprising a ligand binding domain, wherein the ligand binding domain is specific for a ligand, wherein the ligand is a tumor specific molecule, viral specific molecule, or any other selected molecule expressed on a target cell population, wherein the ligand can elicit recognition, modulation, inhibition, and/or elimination by a lymphocyte, a spacer domain, a transmembrane domain, and an

intracellular signaling domain under control of the inducible promoter as described herein. In other alternatives, CD8+ cells have a cytokine or chemokine receptor under the control of an inducible promoter.

[0273] The drug inducible promoter in both modified CD4+ T cells and modified CD8+ cytotoxic T cells can be the same or different. In some alternatives, in one population of cells the promoter linked to the chimeric antigen receptor is a constitutive promoter and in the other population it is an inducible promoter. For example, modified CD4+ T cells that have a chimeric receptor comprising a ligand binding domain specific for a tumor cell surface molecule, a spacer domain, a transmembrane domain, and an intracellular signaling domain under control of an constitutive promoter, while the CD8+ cytotoxic T cell comprises CD8+ cells that have a chimeric receptor comprising a ligand binding domain specific for a tumor cell surface molecule, a spacer domain, a transmembrane domain, and an intracellular signaling domain under control of the inducible promoter. In some alternatives, the genes being controlled by the constitutive or inducible promoter are genes encoding cytokines, chemokine receptors and apoptosis regulators.

[0274] In some alternatives, the polynucleotide can code for a chimeric antigen receptor that differs in the CD4+ versus the CD8+ cell population. The difference between the two constructs can include the specificity or affinity of the ligand binding domain for an antigen or epitope, the length and sequence of the spacer region, and the intracellular signaling components.

[0275] The preparation of the CD4+ and CD8+ cells that are modified with a chimeric receptor is described throughout this disclosure. Antigen specific T lymphocytes can be obtained from a patient having the disease or disorder or can be prepared by in vitro stimulation of T lymphocytes in the presence of antigen. Subpopulations of CD4+ and/or CD8+ T lymphocytes that are not selected for antigen specificity can also be isolated as described herein and combined in the methods of manufacturing.

[0276] In some alternatives, the combination of cell populations can be evaluated for uniformity of cell surface makers, the ability to proliferate through at least two generations, to have a uniform cell differentiation status. Quality control can be performed by co-culturing a cell line expressing the target ligand with chimeric receptor modified T cells and the drug that induces expression of the chimeric antigen receptor to determine if the

chimeric receptor modified T cells recognize the cell line using cytotoxicity, proliferation, or cytokine production assays in the presence of the inducer that are known in the field. Cell differentiation status and cell surface markers on the chimeric receptor modified T cells can be determined by flow cytometry. In some alternatives, the markers and cell differentiation status on the CD8+ cells include CD3, CD8, CD62L, CD28, CD27, CD69, CD25, PD-1, CTLA-4, CD45RO, and/or CD45RA. In some alternatives, the markers and the cell differentiation status on the CD4+ cells include CD3, CD4, CD62L, CD28, CD27, CD69, CD25, PD-1, CTLA-4 CD45RO, and/or CD45RA.

[0277] In some alternatives, the chimeric receptor modified T cells as described herein are able to persist *in vivo* for at least 3 days, or at least 10 days. In some alternatives, the chimeric receptor modified T cells as described herein, can proliferate *in vivo* through at least 2, or at least 3 generations as determined by CFSE dye dilution. Proliferation and persistence of the chimeric receptor modified T cells can be determined by using an animal model of the disease or disorder and administering the cells and determining persistence and/or proliferative capacity of the transferred cells. In other alternatives, proliferation and activation can be tested *in vitro* by going through multiple cycles of activation with antigen bearing cells.

[0278] The disclosure also provides methods of performing cellular immunotherapy in a subject having a disease or disorder comprising: administering a composition of lymphocytes expressing a chimeric receptor under the control of a drug inducible promoter as described herein, and administering the drug.

[0279] In some alternatives, the drug is tamoxifen, variants, derivatives, pharmaceutical salts, solvates, and hydrates thereof as described herein. In some alternatives, the drug is delivered prior to, at the same time as the composition, or at later time points after the composition has been administered.

[0280] In some alternatives, the drug is administered with the composition, and if a toxic effect of the composition is observed the drug is withdrawn until the toxic effects diminish. After the symptoms of toxicity diminish, the drug is administered again. In some alternatives, a drug can be administered again once symptoms of toxicity diminish.

[0281] In some alternatives, the drug is administered with the composition but once the subject has a decrease in the tumor load or cancer cells, the drug is withdrawn for a

period of time to allow the modified cells to rest and if there is no activity of the modified cells, the modified cells are not needed because of remission of the cancer.

[0282] In other alternatives, a method comprises administering to the subject a genetically modified cytotoxic T lymphocyte cell preparation that provides a cellular immune response, wherein the cytotoxic T lymphocyte cell preparation comprises CD8 + T cells that have a chimeric receptor comprising a ligand binding domain, wherein the ligand binding domain is specific for a ligand, wherein the ligand is a tumor specific molecule, viral molecule, or any other molecule expressed on a target cell population, wherein the ligand can elicit recognition, modulation, inhibition, and/or elimination by a lymphocyte, a spacer domain, a transmembrane domain, and an intracellular signaling domain under the control of a drug inducible promoter as described herein, and/or a genetically modified helper T lymphocyte cell preparation that elicits direct tumor recognition and enhances the genetically modified cytotoxic T lymphocyte cell preparations ability to mediate a cellular immune response, wherein the helper T lymphocyte cell preparation comprises CD4+ T cells that have a chimeric receptor comprising a ligand binding domain, wherein the ligand binding domain is specific for a ligand, wherein the ligand is a tumor specific molecule, viral specific molecule, or any other molecule expressed on a target cell population, wherein the ligand can elicit recognition, modulation, inhibition, and/or elimination by a lymphocyte, a spacer domain, a transmembrane domain, and an intracellular signaling domain under control of a constitutive or drug inducible promoter as described herein and administering the drug that induces the inducible promoter. In some alternatives, the administering of the drug is performed after administering of the composition or host cells, wherein administering is performed 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 2 weeks, 4 weeks or two months, or any time in between any two values of time listed. In some alternatives of the methods, the systems are inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor.

[0283] In other alternatives, a method comprises administering to the subject a genetically modified cytotoxic T lymphocyte cell preparation that provides a cellular immune response, wherein the cytotoxic T lymphocyte cell preparation comprises CD8 + T cells that have a chimeric receptor comprising a ligand binding domain specific for a tumor

cell surface molecule, a spacer domain, a transmembrane domain, and an intracellular signaling domain under the control of a constitutive promoter as described herein, and/or a genetically modified helper T lymphocyte cell preparation that elicits direct tumor recognition and enhances the genetically modified cytotoxic T lymphocyte cell preparations ability to mediate a cellular immune response, wherein the helper T lymphocyte cell preparation comprises CD4+ T cells that have a chimeric receptor comprising a ligand binding domain specific for a tumor cell surface molecule, a spacer domain, a transmembrane domain, and an intracellular signaling domain under control of a constitutive or drug inducible promoter as described herein and administering the drug that induces the inducible promoter. In some alternatives, the tumor specific molecule is a tumor surface molecule.

[0284] In other alternatives, a method comprises administering to the subject a genetically modified cytotoxic T lymphocyte cell preparation that provides a cellular immune response, wherein the cytotoxic T lymphocyte cell preparation comprises CD8 + T cells that express a cytokine, chemokine receptor, a polypeptide that regulates apoptosis, and/or a polypeptide that modulates checkpoint signaling under the control of an inducible promoter as described herein, and/or a genetically modified helper T lymphocyte cell preparation that elicits direct tumor recognition and enhances the genetically modified cytotoxic T lymphocyte cell preparations ability to mediate a cellular immune response, wherein the helper T lymphocyte cell preparation comprises CD4+ T cells that express a cytokine, chemokine receptor, a polypeptide that regulates apoptosis, and/or a polypeptide that modulates checkpoint signaling under control of a constitutive or drug inducible promoter as described herein and administering the drug that induces the inducible promoter. In some alternatives, one or more of the cell populations expresses a chimeric antigen receptor under the control of a constitutive promoter. In some alternatives, the modulation of checkpoint signaling inhibits negative checkpoint regulators. In some alternatives, the negative checkpoint regulator comprises PD-1, VISTA, LAG-3 and/or TIM3.

[0285] An effective amount of the drug for induction is an amount of the drug that provides for induction of the chimeric antigen receptor in at least 5 %, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100% or any number in between a range defined by any of the listed

percent values of the transduced cells as described herein. In the methods provided herein, the systems are inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor.

[0286] Another alternative describes a method of performing cellular immunotherapy in a subject having a disease or disorder comprising: analyzing a biological sample of the subject for the presence of a target molecule associated with the disease or disorder and administering the adoptive immunotherapy compositions described herein and administering the drug that induces the inducible promoter, wherein the chimeric receptor specifically binds to the target molecule.

[0287] Subjects that can be treated in accordance with alternatives described herein are, in general, human and other primate subjects, such as monkeys and apes for veterinary medicine purposes. The subjects can be male or female and can be any suitable age, including infant, juvenile, adolescent, adult, and geriatric subjects.

[0288] The methods are useful in the treatment or inhibition of, for example, hematologic malignancy, melanoma, breast cancer, brain cancer, and other epithelial malignancies or solid tumors. In some alternatives, the molecule associated with the disease or disorder is an orphan tyrosine kinase receptor ROR1, Her2, EGFR, CE7, hB7H3, CD19, CD20, CD22, mesothelin, CEA, or a hepatitis B surface antigen.

[0289] Subjects that can be addressed using the methods described herein include subjects identified or selected as having cancer, including but not limited to colon, lung, liver, breast, renal, prostate, ovarian, skin (including melanoma), bone, and brain cancer, etc. Such identification and/or selection can be made by clinical or diagnostic evaluation. In some alternatives, the tumor associated antigens or molecules to which alternatives are directed are antigens associated with melanoma, breast cancer, brain cancer, squamous cell carcinoma, colon cancer, leukemia, myeloma, and/or prostate cancer. In other alternatives the tumor associated molecules can be targeted with genetically modified T cells expressing an engineered chimeric receptor. Examples include but are not limited to B cell lymphoma, breast cancer, brain cancer, prostate cancer, and/or leukemia.

[0290] Cells prepared as described above can be utilized in methods and compositions for adoptive immunotherapy in accordance with known techniques, or

variations thereof that will be apparent to those skilled in the art based on the instant disclosure.

[0291] In some alternatives, the cells are formulated by first harvesting them from their culture medium, and then washing and concentrating the cells in a medium and container system suitable for administration (a "pharmaceutically acceptable" carrier) in a treatment-effective amount. Suitable infusion medium can be any isotonic medium formulation, typically normal saline, Normosol R (Abbott) or Plasma-Lyte A (Baxter), but also 5% dextrose in water or Ringer's lactate can be utilized. The infusion medium can be supplemented with human serum albumin, fetal bovine serum or other human serum components.

[0292] In some alternatives, a treatment or inhibitory effective amount of cells in the composition is a transduced CD4 or CD8 cell or at least 2 cell subsets (for example, 1 CD8+ central memory T cell subset and 1 CD4+ helper T cell subset) or is more typically greater than 10^2 cells, and up to 10^6, up to and including 10^8 or 10^9 cells and can be more than 10^{10} cells. The number of cells will depend upon the ultimate use for which the composition is intended as will the type of cells included therein. For example, if cells that are specific for a particular antigen are desired, then the population will contain greater than 70%, generally greater than 80%, 85% and 90-95% of such cells. For uses provided herein, the cells are generally in a volume of a liter or less, can be 500 mls or less, even 250 mls or 100 mls or less or a volume in between a range defined by any two listed volume values. Hence the density of the desired cells is typically greater than 10^4 cells/m1 and generally is greater than 10^7 cells/ml, generally 10^8 cells/ml or greater. The clinically relevant number of immune cells can be apportioned into multiple infusions that cumulatively equal or exceed 10^6, 10^7, 10^8, 10^8, 10^9, 10^{10} or 10^{11} cells or any amount of cells in between a range defined by any two endpoints of any of the listed values.

[0293] In some alternatives, the lymphocytes of the invention can be used to confer immunity to individuals. "Immunity" has its plain and ordinary meaning when read in light of the specification, and may be used, for example, to mean a lessening of one or more physical symptoms associated with a response to infection by a pathogen, or to a tumor, to which the lymphocyte response is directed. The amount of cells administered is usually in the range present in normal individuals with immunity to the pathogen. Thus, the cells are

usually administered by infusion, with each infusion in a range of from 2 cells, up to at least 10^6 to $3x10^{10}$ cells, preferably in the range of at least 10^7 to 10^9 cells. The T cells can be administered by a single infusion, or by multiple infusions over a range of time. However, since different individuals are expected to vary in responsiveness, the type and amount of cells infused, as well as the number of infusions and the time range over which multiple infusions are given are determined by the attending physician, and can be determined by routine examination. The generation of sufficient levels of T lymphocytes (including cytotoxic T lymphocytes and/or helper T lymphocytes) is readily achievable using the rapid expansion method of the present invention, as exemplified herein.

[0294] In some alternatives, a composition as described herein is administered to an identified or selected subject, such as a subject identified or selected as having melanoma, breast cancer, brain cancer, squamous cell carcinoma, colon cancer, leukemia, myeloma, and/or prostate cancer, intravenously, intraperitoneally, intratumorly, into the bone marrow, into the lymph node, and /or into cerebrospinal fluid. In some alternatives, the chimeric receptor engineered compositions are delivered to the site of the tumor. Alternatively, the compositions as described herein can be combined with a compound that targets the cells to the tumor or the immune system compartments and avoid sites such as the lung.

[0295] In some alternatives, the compositions as described herein are administered with chemotherapeutic agents and/or immunosuppressants. In an alternative, a patient is first administered a chemotherapeutic agent that inhibits or destroys other immune cells followed by the compositions described herein. In some cases, chemotherapy can be avoided entirely.

[0296] In some alternatives, a method comprising administering the modified T cells as described herein in combination with the inducer (e.g. inducible drug) until the tumor burden is diminished. Once the tumor burden is diminished, the inducer drug can be withdrawn in order to switch the expression of the chimeric antigen receptor off and decrease the number of T cells expressing the receptor. In other alternatives, the inducer drug can be administered at a different time in order to switch the expression of the chimeric antigen receptor on in the event of a relapse or increase in tumor growth.

[0297] In other alternatives, the inducer drug can be given for a period of time of days, weeks, or months, and then withdrawn for days, weeks or months, followed by re-

administration of the inducer drug for days, weeks or months to allow for cycling of the expression of the chimeric antigen receptor to avoid anergy or nonresponsiveness due to chronic stimulation of the cells.

More Alternatives.

[0298] In some alternatives, a system for inducible expression of a transgene is provided. In some alternatives, the transgene encodes a chimeric antigen receptor. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, is provided. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis. In some alternatives, genes that inhibit apoptosis include, for example, Bcl2, and/or CA-Akt. In some alternatives, the polypeptide is Bcl2 or CA-Akt. In some alternatives, genes that inhibit apoptosis include, for example, Survivin, Bcl2, CA-Akt, and/or dnCaspase3. In some alternatives, the polypeptide is Survivin, Bcl2, or CA-Akt and/or dnCaspase 3. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK ETNNKKKEFEETVKKVRRAIEQLAAMD). In some alternatives, the polypeptide that regulates apoptosis is Survivin. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124. In some alternatives, Survivin comprises an amino acid sequence set forth in SEQ ID NO: 123. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a transgene, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral specific molecule, and any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a

lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral specific molecule, and any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that

allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with

a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system, the second promoter is an inducible promoter. In some alternatives of the system, the second promoter is a constitutive promoter. In some alternatives of the system, the second promoter is the EF1αp. In some alternatives of the system, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system, the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system, selectable marker is EGFRt and/or HER2t. In some alternatives of the system, the selectable marker confers drug resistance. In some alternatives of the system, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence

identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the chimeric antigen receptor comprises a scFv. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv comprises an huCD19 scFv (G01S) amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 41 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMH WVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDT AVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQ PRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSR SGRAASLIISGLQTEDEADYFCSSYAGRYNSVLFGGGTKLTVL). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 41. In some alternatives, the scFv is encoded by the muCD19 (FMC63) scFv nucleotide sequence. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 42 (Atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccgacatccagatgacccagac cacctccagcctgagcgccagcctgggcgaccgggtgaccatcagctgccgggccagccaggacatcagcaagtacctgaactg gtatcagcagaagcccgacggcaccgtcaagctgctgatctaccacaccagccggctgcacagcggcgtgcccagccggtttagc ggcagcggctccggcaccgactacagcctgaccatctccaacctggaacaggaagatatcgccacctacttttgccagcagggcaa cacactgccctacacctttggcggcggaacaaagctggaaatcaccggcagcacctccggcagcggcaagcctggcagcggcga gggcagcaccaagggcgaggtgaagctgcaggaaagcggccctggcctggtggcccccagccagagcctgagcgtgacctgca ccgtgagcggcgtgagcctgcccgactacggcgtgagctggatccggcagccccccaggaagggcctggaatggctgggcgtga tctggggcagcgagaccacctactacaacagcgccctgaagagccggctgaccatcatcaaggacaacagcaagagccaggtgtt cctgaagatgaacagcctgcagaccgacgacaccgccatctactactgcgccaagcactactactacggcggcagctacgccatgg actactggggccagggcaccagcgtgaccgtgagcagc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 43 (MLLLVTSLLLCELPHPAFLLIPDIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWY QQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLP YTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVSGVS LPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSL

QTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 43. some alternatives, the scFv comprises a B7H3 (hBRCA84D) scFv nucleotide sequence. In some alternatives, the scFv binds specifically to the B7-H3 receptor. In some alternatives, the scFv comprises the L1CAM (CE7) scFv nucleotide sequence. In some alternatives, the scFv is specific for the epitope, CE7 epitope, of L1CAM. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 50

(atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggtgcagctgcagcagcct ggcgccgagctggtgaagccaggcgccagcgtgaagctgtcctgcaaggccagcggctacaccttcaccggctactggatgcact gggtgaagcagagacccggccacggcctggaatggatcggcgagatcaaccccagcaacggccggaccaactacaacgagcgg ttcaagagcaaggccaccctgaccgtggacaagagcagcaccaccgccttcatgcagctgtccggcctgaccagcgaggacagcg ccgtgtacttctgcgccagggactactacggcaccagctacaacttcgactactggggccagggcaccacactgaccgtgagcagc ggcggaggggctctggcggcggaggatctgggggaggggcagcgacatccagatgacccagagcagcagcagcttcagcg tgagcctgggcgaccgggtgaccatcacctgtaaggccaacgaggacatcaacaaccggctggcctggtatcagcagacccccgg caacagccccaggctgctgatcagcggcgccaccaacctggtgaccggcgtgcccagccggtttagcggcagcggctccggcaa ggactacaccctgaccatcacaagcctgcaggccgaggacttcgccacctactactgccagcagtactggtccacccccttcaccttc ggcagcggcaccgagctggaaatcaaa). In some alternatives, the scFv comprises the L1CAM (CE7) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 51

(MLLLVTSLLLCELPHPAFLLIPQVQLQQPGAELVKPGASVKLSCKASGYTFTGYWM HWVKQRPGHGLEWIGEINPSNGRTNYNERFKSKATLTVDKSSTTAFMQLSGLTSEDS AVYFCARDYYGTSYNFDYWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSSSSFS VSLGDRVTITCKANEDINNRLAWYQQTPGNSPRLLISGATNLVTGVPSRFSGSGSGK DYTLTITSLQAEDFATYYCQQYWSTPFTFGSGTELEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 51. In some alternatives, the scFv is encoded by the EGFR (cetuximab) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 52

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtgcagctgaaacagagcg

gcccgggcctggtgcagccgagccagagcctgagcattacctgcaccgtgagcggctttagcctgaccaactatggcgtgcattgg gtgcgccagagcccgggcaaaggcctggaatggctgggcgtgatttggagcggcggcaacaccgattataacaccccgtttacca gccgcctgagcattaacaaagataacagcaaaagccaggtgtttttttaaaatgaacagcctgcagagcaacgataccgcgatttattat tgcgcgcgcgcgctgacctattatgattatgaatttgcgtattggggccagggcaccctggtgaccgtgagcgcgggcggcggcgg cagcggcggcggcggcagcggcggcggcggcagcgatattctgctgacccagagcccggtgattctgagcgtgagcccgggcg aacgcgtgagctttagctgccgcgcgagccagagcattggcaccaacattcattggtatcagcagcgcaccaacggcagcccgcgc ctgctgattaaatatgcgagcgaaagcattagcggcattccgagccgctttagcggcagcggcagcggcaccgattttaccctgagc attaacagcgtggaaagcgaagatattgcggattattattgccagcagaacaacaactggccgaccacctttggcgcgggcaccaaa ctggaactgaaacgcacc). In some alternatives, the scFv comprises the EGFR scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 53 (MLLLVTSLLLCELPHPAFLLIPQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHW VRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIY YCARALTYYDYEFAYWGQGTLVTVSAGGGGSGGGGSGGGGSDILLTQSPVILSVSP GERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSI NSVESEDIADYYCQQNNNWPTTFGAGTKLELKRT). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 53. In some alternatives, the scFv comprises the EGFRVIII (806) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by the EphA2 (2A4) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 56. In some alternatives, the scFv is encoded by the EpHA2 (4H5) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 58. In some alternatives, the scFv is encoded by a FITC (E2) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 60. In some alternatives, the scFv is encoded by an IL13Ra2 (hu08) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 68. In some alternatives, the scFv comprises an IL13Ra2 hu08 VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 69 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFSRNGMS

WVRQAPGKGLEWVATVSSGGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDT
AVYYCARQGTTALATRFFDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSS
LSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIYSASYRSTGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQHHYSAPWTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 69. In some alternatives, the scFv is encoded by an IL13Ra2 (hu07) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 70 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatattcagatgacccagagccc
gagcagcctgagcgcgagcgtgggcgatcgcgtgaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggt
atcagcagaaaccgggcaaagcgccgaaactgctgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcgg
cagcggcagcggcaccgattttaccctgaccattagcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgca
gcccgctgacctttggcggcggcaccaaagtggaaattaaaggtggtggtggttctggcggcggcggctccggtggtggtggttctg
aagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacct
ttaccaaatatggcgtgcattgggtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagca
ccgattataacagcgcgctgatgagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgc
gcgcggaagataccgcggtgtattattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtg
agcagcgaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 71 (MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCTASLSVSSTYLHWY
QQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCHQYHRSP
LTFGGGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFT
KYGVHWVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNS
LRAEDTAVYYCARDHRDAMDYWGQGTLVTVSSESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 71. In some alternatives, the scFv is encoded by the IL13Ra2 (hu07) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 72 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagaagtgcagctggtggaaagcg
gcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacctttaccaaatatggcgtgcattgg

gtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagcaccgattataacagcgcgctgat gagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgcgcgcggaagataccgcggtgt attattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtgagcagcggtggtggtggttctg gcggcggcggctccggtggtggtggttctgatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatcgcgt gaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggtatcagcagaaaccgggcaaagcgccgaaactgc tgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcggcagcggcagcggcaccgattttaccctgaccatta gcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgcagcccgctgacctttggcggcggcaccaaagtgga aattaaagaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 73 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFTKYGVH WVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNSLRAED TAVYYCARDHRDAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCTASLSVSSTYLHWYQQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCHQYHRSPLTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 73. In some alternatives, the antibody or portion thereof or scFv is encoded by the Anti-IL13Ra2 (IL13 zetakine) nucleotide sequence. In some alternatives, the antibody or portion thereof or scFv is encoded by a sequence set forth in SEQ ID NO: 74 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaggccctgtgcctccctctacagcc ctcaggtacctcattgaggagctggtcaacatcacccagaaccagaaggctccgctctgcaatggcagcatggtatggagcatcaac ctgacagctggcatgtactgtgcagccctggaatccctgatcaacgtgtcaggctgcagtgccatcgagaagacccagaggatgctg agcggattctgcccgcacaaggtctcagctgggcagttttccagcttgcatgtccgagacaccaaaatcgaggtggcccagtttgtaa aggacctgctcttacatttaaagaaacttttcgcgagggacggttcaa). In some alternatives, the antibody or portion thereof or scFv comprises an Anti-IL13Ra2 (IL13 zetakine) amino acid sequence. In some alternatives, the antibody or portion thereof or scFv comprises an amino acid sequence set forth in SEQ ID NO: 75 (MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSI NLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQ FVKDLLLHLKKLFREGRF). In some alternatives, the scFv is encoded by a nucleic acid

sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 75. In some alternatives, the scFv is encoded by an oaGD2 (8B6) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 76

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatgttgtgatgacccaaactcca
ctctccctgcctgtcagtcttggagatcaagcctcaatctcttgcagatctagtcagagccttctaaaaaataatggaaacacctttttaca
ttggtacctgcagaagtcaggccagtctccaaagctccttatctacaaagtttccaaccgactttctggggtcccagacaggttcagtgg
cagtggatcagggacatatttcacactcaagatcagcagagtggaggctgaggatctgggagtttatttctgctctcaaagtacacatat
tccgtacacattcggaggggggaccaagctcgagctgaaacgaggcggaggggctctggcggcggaggatctgggggagggg
gcagcgaggtgaaactggtggagtctggaggaggcttggtgctgcctggggattctctgagactctcctgtgcaacttctgagttcac
cttcactgattactacatgacttgggtccgccagcctccaagaaaggcacttgagtggttgggttttattagaaacagagctaatggttac
acaacagagtacaatccatctgtgaagggtcggttcaccatttccagagataattcccaaagcatcctctatcttcaaatgaacaccctg
agaactgaggacagtgccacttattactgtgcaagagtctctaactgggcctttgactactggggccaaggcaccactctcacagtctc
ctca). In some alternatives, the scFv comprises the oaGD2 (8B6) VlVh scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 77

(MLLLVTSLLLCELPHPAFLLIPDVVMTQTPLSLPVSLGDQASISCRSSQSLLKNNGNT
FLHWYLQKSGQSPKLLIYKVSNRLSGVPDRFSGSGSGTYFTLKISRVEAEDLGVYFCS
QSTHIPYTFGGGTKLELKRGGGGSGGGGSGGGGSEVKLVESGGGLVLPGDSLRLSCA
TSEFTFTDYYMTWVRQPPRKALEWLGFIRNRANGYTTEYNPSVKGRFTISRDNSQSIL
YLQMNTLRTEDSATYYCARVSNWAFDYWGQGTTLTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 77. In some alternatives, the scFv is encoded by an ROR1 (R12) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 78

(atgctgctgctggtgacaagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggaacagctcgtcgaaagc
ggcggcagactggtgacacctggcggcagcctgaccctgagctgcaaggccagcggcttcgacttcagcgcctactacatgagctg
ggtccgccaggcccctggcaagggactggaatggatcgccaccatctaccccagcagcggcaagacctactacgccacctgggtg
aacggacggttcaccatctccagcgacaacgcccagaacaccgtggacctgcagatgaacagcctgacagccgccgaccgggcc
acctacttttgcgccagagacagctacgccgacgacggcgccctgttcaacatctggggccctggcaccctggtgacaatctctagc
ggcggaggcggatctggtggcggaggaagtggcggcggaggatctgagctggtgctgacccagagcccctctgtgtctgctgccc

tgggaagccctgccaagatcacctgtaccctgagcagcgcccacaagaccgacaccatcgactggtatcagcagctgcagggcga ggcccccagatacctgatgcaggtgcagagcgacggcagctacaccaagaggccaggcgtgcccgaccggttcagcggatctag ctctggcgccgaccgctacctgatcatccccagcgtgcaggccgatgacgaggccgattactactgtggcgccgactacatcggcg gctacgtgttcggcggaggcacccagctgaccgtgaccggc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 79 (ROR1 (R12) scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQEQLVESGGRLVTPGGSLTLSCKASGFDFSAYYMSW VRQAPGKGLEWIATIYPSSGKTYYATWVNGRFTISSDNAQNTVDLQMNSLTAADRA TYFCARDSYADDGALFNIWGPGTLVTISSGGGGSGGGGSGGGGSELVLTQSPSVSAA LGSPAKITCTLSSAHKTDTIDWYQQLQGEAPRYLMQVQSDGSYTKRPGVPDRFSGSS SGADRYLIIPSVQADDEADYYCGADYIGGYVFGGGTQLTVTG). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 79. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 80 (CD33 (h2H12) VhVl scFv nucleotide sequence

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggttcagctggtgcagtctgga gctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggttacacctttaccaattatgatataaattgggtgag acaggcccctggacaagggcttgagtggattggatggatttatcctggagatggtagtaccaaatataatgagaaattcaaggccaag gctaccctgacagctgacacatccaccagcacagcctacatggagctgaggagcctgagatctgatgacacagctgtgtattactgtg cttctggatatgaagatgctatggactactgggggcaagggaccacagtcacagtctcctca). In some alternatives, the scFv is specific for CD33. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 81 (CD33 (h2H12) VhVl scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYDIN WVRQAPGQGLEWIGWIYPGDGSTKYNEKFKAKATLTADTSTSTAYMELRSLRSDDT AVYYCASGYEDAMDYWGQGTTVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 81. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 82 (CD33 (h2H12) VlVh scFv nucleotide sequence: atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagacatccagatgacccagtctccat cctcactgtctgcatctgtaggagacagagtcaccatcaattgtaaggctagtcaggacattaatagctatttgagctggtttcagcaga aaccagggaaagcccctaagaccctgatctatagagcaaatagattggtagatggggtcccatcaaggttctctggcagtggatctgg gcaagattatactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgcttgcagtatgatgagtttcctctcacatttgg

aggagggaccaaggtggagatcaaa). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 83 (CD33 (h2H12) VlVh scFv amino acid sequence: MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTINCKASQDINSYLSWFQ QKPGKAPKTLIYRANRLVDGVPSRFSGSGSGQDYTLTISSLQPEDFATYYCLQYDEFP LTFGGGTKVEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 83. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 84. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 86. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 87. In some alternatives, the spacer is encoded by the nucleic acid sequence set forth in SEQ ID NO: 102 (IgG4 hinge nucleotide sequence: gagagcaagtacggaccgccctgccccccttgccct). In some alternatives, the spacer comprises an amino acid sequence set forth in SEQ ID NO: 103 (IgG4 hinge amino acid sequence: ESKYGPPCPPCP). In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 103. In some alternatives, the spacer is encoded by a nucleic acid sequence set forth in SEQ ID NO: 104. In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives, HEA3 comprises two amino acid mutations, wherein the sequence is encoded by a sequence set forth in SEQ ID NO: 122 (atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc

agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag
ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct
gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc
ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccctatcctgtacagcgagtacgaccccaccagacccttcagc
gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc
ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc
atggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga
tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct
gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga
tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc
ctgagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct
gctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca
cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt
ggagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcat
catgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagc
gtgcccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttcccca
gcggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccat
ggtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacct
acccaggccggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaata
gcaccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcc
ccacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccag
caccagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttca
gcgccctgctgtcccagatcagcagc). In some alternatives, the HEA3 comprises an amino acid sequence set forth in SEQ ID NO: 121 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV

WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM
DFSALLSQISS). This sequence comprises the sequence of HEA3 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA3(p65/S536E/K310Q). K310Q in RelA corresponds to position 621 in HEA3; S536E corresponds to position 846 in HEA3. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells is provided. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis. In some alternatives, genes that inhibit apoptosis include, for example, Bcl2, and/or CA-Akt. In some alternatives, the polypeptide is Bcl2 or CA-Akt. In some alternatives, genes that inhibit apoptosis include, for example, Survivin, Bcl2, CA-Akt, and/or dnCaspase3. In some alternatives, the polypeptide is Survivin, Bcl2, or CA-Akt and/or dnCaspase 3. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag
ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt
cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt
ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac
caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC
FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK
ETNNKKKEFEETVKKVRRAIEQLAAMD).

[0299] In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells is provided. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably

linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral specific molecule, and any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer; a third polynucleotide, which encodes a transmembrane domain; and a fourth polynucleotide, which encodes an intracellular signaling domain; and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives, the transcriptional activator is HEA3 or HEA4. In some alternatives, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional

activity in response to the drug ligand. In some alternatives, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives, the second promoter is an inducible promoter. In some alternatives, the second promoter is a constitutive promoter. In some alternatives, the second promoter is the EF1αp. In some alternatives, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives, the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives, both vectors are packaged in a viral vector. In some alternatives, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the first nucleic acid further comprises a fifth polynucleotide that encodes

a selectable marker. In some alternatives, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives, the selectable marker is EGFRt and/or HER2t. In some alternatives, the selectable marker confers drug resistance. In some alternatives, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives, the DNA spacer enhances gene expression of the chimeric antigen receptor.

[0300] In some alternatives, a system for inducible expression of a gene that regulates a T cell function is provided. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some

alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric

transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the second nucleic acid further comprises: a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the system, the first promoter is in opposite orientation to the second promoter. In some alternatives of the system, the ligand binding domain is an antibody fragment. In some alternatives of the system, the ligand binding domain is a single chain variable fragment. In some alternatives of the system, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof. In some alternatives of the system, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the system, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives of the system, the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that

encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the chimeric antigen receptor comprises a scFv. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv comprises an huCD19 scFv (G01S) amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 41 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMH WVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDT AVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQ PRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSR SGRAASLIISGLQTEDEADYFCSSYAGRYNSVLFGGGTKLTVL). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 41. In some alternatives, the scFv is encoded by the muCD19 (FMC63) scFv nucleotide sequence. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 42 (Atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccgacatccagatgacccagac cacctccagcctgagcgccagcctgggcgaccgggtgaccatcagctgccgggccagccaggacatcagcaagtacctgaactg gtatcagcagaagcccgacggcaccgtcaagctgctgatctaccacaccagccggctgcacagcggcgtgcccagccggtttagc ggcagcggctccggcaccgactacagcctgaccatctccaacctggaacaggaagatatcgccacctacttttgccagcagggcaa cacactgccctacacctttggcggcggaacaaagctggaaatcaccggcagcacctccggcagcggcaagcctggcagcggcga gggcagcaccaagggcgaggtgaagctgcaggaaagcggccctggcctggtggcccccagccagagcctgagcgtgacctgca

ccgtgagcggcgtgagcctgcccgactacggcgtgagctggatccggcagccccccaggaagggcctggaatggctgggcgtga tctggggcagcgagaccacctactacaacagcgccctgaagagccggctgaccatcatcaaggacaacagcaagagccaggtgtt cctgaagatgaacagcctgcagaccgacgacaccgccatctactactgcgccaagcactactactacggcggcagctacgccatgg actactggggccagggcaccagcgtgaccgtgagcagc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 43 (MLLLVTSLLLCELPHPAFLLIPDIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWY QQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLP YTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVSGVS LPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSL QTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 43. some alternatives, the scFv comprises a B7H3 (hBRCA84D) scFv nucleotide sequence. In some alternatives, the scFv binds specifically to the B7-H3 receptor. In some alternatives, the scFv comprises the L1CAM (CE7) scFv nucleotide sequence. In some alternatives, the scFv is specific for the epitope, CE7 epitope, of L1CAM. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 50

(atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccaggtgcagctgcagcagcct ggcgccgagctggtgaagccaggcgccagcgtgaagctgtcctgcaaggccagcggctacaccttcaccggctactggatgcact gggtgaagcagagacccggccacggcctggaatggatcggcgagatcaaccccagcaacggccggaccaactacaacgagcgg ttcaagagcaaggccaccctgaccgtggacaagagcagcaccaccgccttcatgcagctgtccggcctgaccagcgaggacagcg ccgtgtacttctgcgccagggactactacggcaccagctacaacttcgactactggggccagggcaccacactgaccgtgagcagc ggcggaggggggctctggcggcggaggatctgggggaggggggcagcgacatccagatgacccagagcagcagcagcttcagcg tgagcctgggcgaccgggtgaccatcacctgtaaggccaacgaggacatcaacaaccggctggcctggtatcagcagacccccgg caacagccccaggctgctgatcagcggcgccaccaacctggtgaccggcgtgcccagccggtttagcggcagcggctccggcaa ggactacaccctgaccatcacaagcctgcaggccgaggacttcgccacctactactgccagcagtactggtccacccccttcaccttc ggcagcggcaccgagctggaaatcaaa). In some alternatives, the scFv comprises the L1CAM (CE7) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 51 (MLLLVTSLLLCELPHPAFLLIPQVQLQQPGAELVKPGASVKLSCKASGYTFTGYWM HWVKQRPGHGLEWIGEINPSNGRTNYNERFKSKATLTVDKSSTTAFMQLSGLTSEDS

AVYFCARDYYGTSYNFDYWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSSSSFS
VSLGDRVTITCKANEDINNRLAWYQQTPGNSPRLLISGATNLVTGVPSRFSGSGSGK
DYTLTITSLQAEDFATYYCQQYWSTPFTFGSGTELEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 51. In some alternatives, the scFv is encoded by the EGFR (cetuximab) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 52 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtgcagctgaaacagagcg gcccgggcctggtgcagccgagccagagcctgagcattacctgcaccgtgagcggctttagcctgaccaactatggcgtgcattgg gtgcgccagagcccgggcaaaggcctggaatggctgggcgtgatttggagcggcggcaacaccgattataacaccccgtttacca gccgcctgagcattaacaaagataacagcaaaagccaggtgtttttaaaatgaacagcctgcagagcaacgataccgcgatttattat tgcgcgcgcgcgctgacctattatgattatgaatttgcgtattggggccagggcaccctggtgaccgtgagcgcgggcggcggcgg cagcggcggcggcggcagcggcggcggcggcagcgatattctgctgacccagagcccggtgattctgagcgtgagcccgggcg aacgcgtgagctttagctgccgcgcgagccagagcattggcaccaacattcattggtatcagcagcgcaccaacggcagcccgcgc ctgctgattaaatatgcgagcgaaagcattagcggcattccgagccgctttagcggcagcggcagcggcaccgattttaccctgagc attaacagcgtggaaagcgaagatattgcggattattattgccagcagaacaacaactggccgaccacctttggcgcgggcaccaaa ctggaactgaaacgcacc). In some alternatives, the scFv comprises the EGFR scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 53 (MLLLVTSLLLCELPHPAFLLIPQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHW
VRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIY
YCARALTYYDYEFAYWGQGTLVTVSAGGGGSGGGGSGGGGSDILLTQSPVILSVSP
GERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSI
NSVESEDIADYYCQQNNNWPTTFGAGTKLELKRT). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 53. In some alternatives, the scFv comprises the EGFRVIII (806) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by the EphA2 (2A4) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 56. In some alternatives, the scFv is encoded by the EpHA2 (4H5) scFv nucleotide sequence. In

some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 58. In some alternatives, the scFv is encoded by a FITC (E2) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 60. In some alternatives, the scFv is encoded by an IL13Ra2 (hu08) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 68. In some alternatives, the scFv comprises an IL13Ra2 hu08 VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 69 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFSRNGMS WVRQAPGKGLEWVATVSSGGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARQGTTALATRFFDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSS LSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIYSASYRSTGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQHHYSAPWTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 69. In some alternatives, the scFv is encoded by an IL13Ra2 (hu07) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 70 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatattcagatgacccagagccc gagcagcctgagcgcgagcgtgggcgatcgcgtgaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggt atcagcagaaaccgggcaaagcgccgaaactgctgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcgg cagcggcagcggcaccgattttaccctgaccattagcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgca gcccgctgacctttggcggcggcaccaaagtggaaattaaaggtggtggttctggcggcggcggctccggtggtggtggttctg aagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacct ttaccaaatatggcgtgcattgggtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagca ccgattataacagcgcgctgatgagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgc gcgcggaagataccgcggtgtattattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtg agcagcgaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 71 (MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCTASLSVSSTYLHWY QQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCHQYHRSP

LTFGGGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFT KYGVHWVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARDHRDAMDYWGQGTLVTVSSESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 71. In some alternatives, the scFv is encoded by the IL13Ra2 (hu07) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 72 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagaagtgcagctggtggaaagcg gcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacctttaccaaatatggcgtgcattgg gtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagcaccgattataacagcgcgctgat gagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgcgcgcggaagataccgcggtgt attattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtgagcagcggtggtggtggttctg gcggcggcggctccggtggtggtggttctgatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatcgcgt gaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggtatcagcagaaaccgggcaaagcgccgaaactgc tgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcggcagcggcagcggcaccgattttaccctgaccatta gcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgcagcccgctgacctttggcggcggcaccaaagtgga aattaaagaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 73 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFTKYGVH WVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNSLRAED TAVYYCARDHRDAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCTASLSVSSTYLHWYQQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCHQYHRSPLTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 73. In some alternatives, the antibody or portion thereof or scFv is encoded by the Anti-IL13Ra2 (IL13 zetakine) nucleotide sequence. In some alternatives, the antibody or portion thereof or scFv is encoded by a sequence set forth in SEQ ID NO: 74 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaggccctgtgcctccctctacagcc ctcaggtacctcattgaggagctggtcaacatcacccagaaccagaaggctccgctctgcaatggcagcatggtatggagcatcaac

ctgacagctggcatgtactgtgcagccctggaatccctgatcaacgtgtcaggctgcagtgccatcgagaagacccagaggatgctg agcggattctgcccgcacaaggtctcagctgggcagttttccagcttgcatgtccgagacaccaaaatcgaggtggcccagtttgtaa aggacctgctcttacatttaaagaaacttttcgcgagggacggttcaa). In some alternatives, the antibody or portion thereof or scFv comprises an Anti-IL13Ra2 (IL13 zetakine) amino acid sequence. In some alternatives, the antibody or portion thereof or scFv comprises an amino acid sequence set forth in SEQ ID NO: 75 (MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSI NLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQ FVKDLLLHLKKLFREGRF). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 75. In some alternatives, the scFv is encoded by an oaGD2 (8B6) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 76

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatgttgtgatgacccaaactcca ctctccctgcctgtcagtcttggagatcaagcctcaatctcttgcagatctagtcagagccttctaaaaaataatggaaacacctttttaca ttggtacctgcagaagtcaggccagtctccaaagctccttatctacaaagtttccaaccgactttctggggtcccagacaggttcagtgg cagtggatcagggacatatttcacactcaagatcagcagagtggaggctgaggatctgggagtttatttctgctctcaaagtacacatat tccgtacacattcggaggggggaccaagctcgagctgaaacgaggcggaggggctctggcggcggaggatctgggggagggg gcagcgaggtgaaactggtggagtctggaggaggcttggtgctgcctggggattctctgagactctcctgtgcaacttctgagttcac cttcactgattactacatgacttgggtccgccagcctccaagaaaggcacttgagtggttgggttttattagaaacagagctaatggttac acaacagagtacaatccatctgtgaagggtcggttcaccatttccagagataattcccaaagcatcctctatcttcaaatgaacaccctg agaactgaggacagtgccacttattactgtgcaagagtctctaactgggcctttgactactggggccaaggcaccactctcacagtctc ctca). In some alternatives, the scFv comprises the oaGD2 (8B6) VlVh scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 77 (MLLLVTSLLLCELPHPAFLLIPDVVMTQTPLSLPVSLGDQASISCRSSQSLLKNNGNT FLHWYLQKSGQSPKLLIYKVSNRLSGVPDRFSGSGSGTYFTLKISRVEAEDLGVYFCS QSTHIPYTFGGGTKLELKRGGGGSGGGGSGGGGSEVKLVESGGGLVLPGDSLRLSCA TSEFTFTDYYMTWVRQPPRKALEWLGFIRNRANGYTTEYNPSVKGRFTISRDNSQSIL YLQMNTLRTEDSATYYCARVSNWAFDYWGQGTTLTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the

amino acid sequence of SEQ ID NO: 77. In some alternatives, the scFv is encoded by an ROR1 (R12) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 78 (atgctgctgctggtgacaagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggaacagctcgtcgaaagc ggcggcagactggtgacacctggcggcagcctgaccctgagctgcaaggccagcggcttcgacttcagcgcctactacatgagctg ggtccgccaggcccctggcaagggactggaatggatcgccaccatctaccccagcagcggcaagacctactacgccacctgggtg aacggacggttcaccatctccagcgacaacgcccagaacaccgtggacctgcagatgaacagcctgacagccgccgaccgggcc acctacttttgcgccagagacagctacgccgacgacggcgccctgttcaacatctggggccctggcaccctggtgacaatctctagc ggcggaggcggatctggtggcggaggaagtggcggcggaggatctgagctggtgctgacccagagcccctctgtgtctgctgccc tgggaagccctgccaagatcacctgtaccctgagcagcgcccacaagaccgacaccatcgactggtatcagcagctgcagggcga ggcccccagatacctgatgcaggtgcagagcgacggcagctacaccaagaggccaggcgtgcccgaccggttcagcggatctag ctctggcgccgaccgctacctgatcatccccagcgtgcaggccgatgacgaggccgattactactgtggcgccgactacatcggcg gctacgtgttcggcggaggcacccagctgaccgtgaccggc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 79 (ROR1 (R12) scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQEQLVESGGRLVTPGGSLTLSCKASGFDFSAYYMSW VRQAPGKGLEWIATIYPSSGKTYYATWVNGRFTISSDNAQNTVDLQMNSLTAADRA TYFCARDSYADDGALFNIWGPGTLVTISSGGGGSGGGGSGGGGSELVLTQSPSVSAA LGSPAKITCTLSSAHKTDTIDWYQQLQGEAPRYLMQVQSDGSYTKRPGVPDRFSGSS SGADRYLIIPSVQADDEADYYCGADYIGGYVFGGGTQLTVTG). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 79. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 80 (CD33 (h2H12) VhVl scFv nucleotide sequence

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggttcagctggtgcagtctgga gctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggttacacctttaccaattatgatataaattgggtgag acaggcccctggacaagggcttgagtggattggatggatttatcctggagatggtagtaccaaatataatgagaaattcaaggccaag gctaccctgacagctgacacatccaccagcacagcctacatggagctgaggagcctgagatctgatgacacagctgtgtattactgtg cttctggatatgaagatgctatggactactgggggcaagggaccacagtcacagtctcctca). In some alternatives, the scFv is specific for CD33. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 81 (CD33 (h2H12) VhVl scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYDIN

WVRQAPGQGLEWIGWIYPGDGSTKYNEKFKAKATLTADTSTSTAYMELRSLRSDDT AVYYCASGYEDAMDYWGQGTTVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 81. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 82 (CD33 (h2H12) VlVh scFv nucleotide sequence: atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagacatccagatgacccagtctccat cctcactgtctgcatctgtaggagacagagtcaccatcaattgtaaggctagtcaggacattaatagctatttgagctggtttcagcaga aaccagggaaagcccctaagaccctgatctatagagcaaatagattggtagatggggtcccatcaaggttctctggcagtggatctgg gcaagattatactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgcttgcagtatgatgagtttcctctcacatttgg aggagggaccaaggtggagatcaaa). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 83 (CD33 (h2H12) VlVh scFv amino acid sequence: MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTINCKASQDINSYLSWFQ QKPGKAPKTLIYRANRLVDGVPSRFSGSGSGQDYTLTISSLQPEDFATYYCLQYDEFP LTFGGGTKVEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 83. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 84. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 86. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 87. In some alternatives, the spacer is encoded by the nucleic acid sequence set forth in SEQ ID NO: 102 (IgG4 hinge nucleotide sequence: gagagcaagtacggaccgccctgccccccttgccct). In some alternatives, the spacer comprises an amino acid sequence set forth in SEQ ID NO: 103 (IgG4 hinge amino acid sequence: ESKYGPPCPPCP). In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 103. In some alternatives, the spacer is encoded by a nucleic acid sequence set forth in SEQ ID NO: 104. In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives, HEA3 comprises two amino

acid mutations, wherein the sequence is encoded by a sequence set forth in SEQ ID NO: 122 (atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagc gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc atggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc ctgagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct gctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt ggagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcat catgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagc gtgcccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttcccca gcggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccat ggtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacct acccaggccggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaata gcaccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcc ccacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccag caccagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttca

gcgccctgctgtcccagatcagcagc). In some alternatives, the HEA3 comprises an amino acid sequence set forth in SEQ ID NO: 121 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM DFSALLSQISS). This sequence comprises the sequence of HEA3 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA3(p65/S536E/K310Q). K310Q in RelA corresponds to position 621 in HEA3; S536E corresponds to position 846 in HEA3. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells is provided. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis. In some alternatives, genes that inhibit apoptosis include, for example, Bcl2, and/or CA-Akt. In some alternatives, the polypeptide is Bcl2 or CA-Akt. In some alternatives, genes that inhibit apoptosis include, for example, Survivin, Bcl2, CA-Akt, and/or dnCaspase3. In some alternatives, the polypeptide is Survivin, Bcl2, or CA-Akt and/or dnCaspase 3. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt

ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK ETNNKKKEFEETVKKVRRAIEQLAAMD). In some alternatives, a system for inducible expression of a transgene in cells is provided. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis. In some alternatives, genes that inhibit apoptosis include, for example, Bcl2, and/or CA-Akt. In some alternatives, the polypeptide is Bcl2 or CA-Akt. In some alternatives, genes that inhibit apoptosis include, for example, Survivin, Bcl2, CA-Akt, and/or dnCaspase3. In some alternatives, the polypeptide is Survivin, Bcl2, or CA-Akt and/or dnCaspase 3. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK ETNNKKKEFEETVKKVRRAIEQLAAMD).

[0301] In some alternatives, a chimeric receptor polypeptide coded for by the first nucleic acid of the system of any one of the alternatives herein or the second nucleic acid of the system of any one of the alternatives is provided. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells, The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral specific molecule, and any other selected molecule expressed on a target cell population, wherein the

ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives

of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system, the second promoter is an inducible promoter. In some alternatives of the system, the second promoter is a constitutive promoter. In some alternatives of the system, the second promoter is the EF1αp. In some alternatives of the system, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system, the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system, the first nucleic acid further comprises a fifth

polynucleotide that encodes a selectable marker. In some alternatives of the system, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system, selectable marker is EGFRt and/or HER2t. In some alternatives of the system, the selectable marker confers drug resistance. In some alternatives of the system, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to

a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the drug induces a level of

expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the second nucleic acid further comprises: a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the system, the first promoter is in opposite orientation to the second promoter. In some alternatives of the system, the ligand binding domain is an antibody fragment. In some alternatives of the system, the ligand binding domain is a single chain variable fragment. In some alternatives of the system, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof. In some alternatives of the system, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the system, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC or VAR2CSA. In some alternatives of the system, the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3. In some alternatives of the system, the first nucleic acid

further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the chimeric antigen receptor comprises a scFv. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv comprises an huCD19 scFv (G01S) amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 41 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMH WVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDT AVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQ PRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSR SGRAASLIISGLQTEDEADYFCSSYAGRYNSVLFGGGTKLTVL). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 41. In some alternatives, the scFv is encoded by the muCD19 (FMC63) scFv nucleotide sequence. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 42 (Atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccgacatccagatgacccagac cacctccagcctgagcgccagcctgggcgaccgggtgaccatcagctgccgggccagccaggacatcagcaagtacctgaactg gtatcagcagaagcccgacggcaccgtcaagctgctgatctaccacaccagccggctgcacagcggcgtgcccagccggtttagc ggcagcggctccggcaccgactacagcctgaccatctccaacctggaacaggaagatatcgccacctacttttgccagcagggcaa cacactgccctacacctttggcggcggaacaaagctggaaatcaccggcagcacctccggcagcggcaagcctggcagcggcga

gggcagcaccaagggcgaggtgaagctgcaggaaagcggccctggcctggtggcccccagccagagcctgagcgtgacctgca ccgtgagcggcgtgagcctgcccgactacggcgtgagctggatccggcagcccccaggaagggcctggaatggctgggcgtga tctggggcagcgagaccacctactacaacagcgccctgaagagccggctgaccatcatcaaggacaacagcaagagccaggtgtt cctgaagatgaacagcctgcagaccgacgacaccgccatctactactgcgccaagcactactactacggcggcagctacgccatgg actactggggccagggcaccagcgtgaccgtgagcagc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 43 (MLLLVTSLLLCELPHPAFLLIPDIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWY QQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLP YTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVSGVS LPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSL QTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 43. some alternatives, the scFv comprises a B7H3 (hBRCA84D) scFv nucleotide sequence. In some alternatives, the scFv binds specifically to the B7-H3 receptor. In some alternatives, the scFv comprises the L1CAM (CE7) scFv nucleotide sequence. In some alternatives, the scFv is specific for the epitope, CE7 epitope, of L1CAM. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 50

(atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccaggtgcagctgcagcagcct ggcgccgagctggtgaagccaggcgccagcgtgaagctgtcctgcaaggccagcggctacaccttcaccggctactggatgcact gggtgaagcagagacccggccacggcctggaatggatcggcgagatcaaccccagcaacggccggaccaactacaacgagcgg ttcaagagcaaggccaccctgaccgtggacaagagcagcaccaccgccttcatgcagctgtccggcctgaccagcgaggacagcg ccgtgtacttctgcgccagggactactacggcaccagctacaacttcgactactggggccagggcaccacactgaccgtgagcagc ggcggaggggggctctggcggcggaggatctgggggaggggggcagcgacatccagatgacccagagcagcagcagcttcagcg tgagcctgggcgaccgggtgaccatcacctgtaaggccaacgaggacatcaacaaccggctggcctggtatcagcagacccccgg caacagccccaggctgctgatcagcggcgccaccaacctggtgaccggcgtgcccagccggtttagcggcagcggctccggcaa ggactacaccctgaccatcacaagcctgcaggccgaggacttcgccacctactactgccagcagtactggtccacccccttcaccttc ggcagcggcaccgagctggaaatcaaa). In some alternatives, the scFv comprises the L1CAM (CE7) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 51 (MLLLVTSLLLCELPHPAFLLIPQVQLQQPGAELVKPGASVKLSCKASGYTFTGYWM

HWVKQRPGHGLEWIGEINPSNGRTNYNERFKSKATLTVDKSSTTAFMQLSGLTSEDS
AVYFCARDYYGTSYNFDYWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSSSSFS
VSLGDRVTITCKANEDINNRLAWYQQTPGNSPRLLISGATNLVTGVPSRFSGSGSGK
DYTLTITSLQAEDFATYYCQQYWSTPFTFGSGTELEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 51. In some alternatives, the scFv is encoded by the EGFR (cetuximab) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 52 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtgcagctgaaacagagcg
gcccgggcctggtgcagccgagccagagcctgagcattacctgcaccgtgagcggctttagcctgaccaactatggcgtgcattgg
gtgcgccagagcccgggcaaaggcctggaatggctgggcgtgatttggagcggcggcaacaccgattataacaccccgtttacca
gccgcctgagcattaacaaagataacagcaaaagccaggtgtttttttaaaatgaacagcctgcagagcaacgataccgcgatttattat
tgcgcgcgcgcgctgacctattatgattatgaatttgcgtattggggccagggcaccctggtgaccgtgagcgcgggcggcggcgg
cagcggcggcggcggcagcggcggcggcggcagcgatattctgctgacccagagcccggtgattctgagcgtgagcccgggcg
aacgcgtgagctttagctgccgcgcgagccagagcattggcaccaacattcattggtatcagcagcgcaccaacggcagcccgcgc
ctgctgattaaatatgcgagcgaaagcattagcggcattccgagccgctttagcggcagcggcagcggcaccgattttaccctgagc
attaacagcgtggaaagcgaagatattgcggattattattgccagcagaacaacaactggccgaccacctttggcgcgggcaccaaa
ctggaactgaaacgcacc). In some alternatives, the scFv comprises the EGFR scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 53 (MLLLVTSLLLCELPHPAFLLIPQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHW
VRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIY
YCARALTYYDYEFAYWGQGTLVTVSAGGGGSGGGGSGGGGSDILLTQSPVILSVSP
GERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSI
NSVESEDIADYYCQQNNNWPTTFGAGTKLELKRT). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 53. In some alternatives, the scFv comprises the EGFRVIII (806) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by the EphA2 (2A4) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 56. In

some alternatives, the scFv is encoded by the EpHA2 (4H5) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 58. In some alternatives, the scFv is encoded by a FITC (E2) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 60. In some alternatives, the scFv is encoded by an IL13Ra2 (hu08) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 68. In some alternatives, the scFv comprises an IL13Ra2 hu08 VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 69 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFSRNGMS WVRQAPGKGLEWVATVSSGGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARQGTTALATRFFDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSS LSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIYSASYRSTGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQHHYSAPWTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 69. In some alternatives, the scFv is encoded by an IL13Ra2 (hu07) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 70 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatattcagatgacccagagccc gagcagcctgagcgcgagcgtgggcgatcgcgtgaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggt atcagcagaaaccgggcaaagcgccgaaactgctgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcgg cagcggcagcggcaccgattttaccctgaccattagcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgca gcccgctgacctttggcggcggcaccaaagtggaaattaaaggtggtggtggttctggcggcggcggctccggtggtggtggttctg aagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacct ttaccaaatatggcgtgcattgggtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagca ccgattataacagcgcgctgatgagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgc gcgcggaagataccgcggtgtattattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtg agcagcgaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 71 (MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCTASLSVSSTYLHWY

QQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCHQYHRSP
LTFGGGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFT
KYGVHWVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNS
LRAEDTAVYYCARDHRDAMDYWGQGTLVTVSSESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 71. In some alternatives, the scFv is encoded by the IL13Ra2 (hu07) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 72 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagaagtgcagctggtggaaagcg gcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacctttaccaaatatggcgtgcattgg gtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagcaccgattataacagcgcgctgat gagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgcgcgcggaagataccgcggtgt attattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtgagcagcggtggtggtggttctg gcggcggcggctccggtggtggtggttctgatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatcgcgt gaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggtatcagcagaaaccgggcaaagcgccgaaactgc tgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcggcagcggcagcggcaccgattttaccctgaccatta gcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgcagcccgctgacctttggcggcggcaccaaagtgga aattaaagaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 73 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFTKYGVH
WVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNSLRAED
TAVYYCARDHRDAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA
SVGDRVTITCTASLSVSSTYLHWYQQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTD
FTLTISSLQPEDFATYYCHQYHRSPLTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 73. In some alternatives, the antibody or portion thereof or scFv is encoded by the Anti-IL13Ra2 (IL13 zetakine) nucleotide sequence. In some alternatives, the antibody or portion thereof or scFv is encoded by a sequence set forth in SEQ ID NO: 74 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaggccctgtgcctccctctacagcc

ctcaggtacctcattgaggagctggtcaacatcacccagaaccagaaggctccgctctgcaatggcagcatggtatggagcatcaac ctgacagctggcatgtactgtgcagccctggaatccctgatcaacgtgtcaggctgcagtgccatcgagaagacccagaggatgctg agcggattctgcccgcacaaggtctcagctgggcagttttccagcttgcatgtccgagacaccaaaatcgaggtggcccagtttgtaa aggacctgctcttacatttaaagaaacttttcgcgagggacggttcaa). In some alternatives, the antibody or portion thereof or scFv comprises an Anti-IL13Ra2 (IL13 zetakine) amino acid sequence. In some alternatives, the antibody or portion thereof or scFv comprises an amino acid sequence set forth in SEQ ID NO: 75 (MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSI NLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQ FVKDLLLHLKKLFREGRF). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 75. In some alternatives, the scFv is encoded by an oaGD2 (8B6) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 76

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatgttgtgatgacccaaactcca ctctccctgcctgtcagtcttggagatcaagcctcaatctcttgcagatctagtcagagccttctaaaaaataatggaaacacctttttaca ttggtacctgcagaagtcaggccagtctccaaagctccttatctacaaagtttccaaccgactttctggggtcccagacaggttcagtgg cagtggatcagggacatatttcacactcaagatcagcagagtggaggctgaggatctgggagtttatttctgctctcaaagtacacatat tccgtacacattcggaggggggaccaagctcgagctgaaacgaggcggaggggctctggcggcggaggatctgggggagggg gcagcgaggtgaaactggtggagtctggaggaggcttggtgctgcctggggattctctgagactctcctgtgcaacttctgagttcac cttcactgattactacatgacttgggtccgccagcctccaagaaaggcacttgagtggttgggttttattagaaacagagctaatggttac acaacagagtacaatccatctgtgaagggtcggttcaccatttccagagataattcccaaagcatcctctatcttcaaatgaacaccctg agaactgaggacagtgccacttattactgtgcaagagtctctaactgggcctttgactactggggccaaggcaccactctcacagtctc ctca). In some alternatives, the scFv comprises the oaGD2 (8B6) VlVh scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 77 (MLLLVTSLLLCELPHPAFLLIPDVVMTQTPLSLPVSLGDQASISCRSSQSLLKNNGNT FLHWYLQKSGQSPKLLIYKVSNRLSGVPDRFSGSGSGTYFTLKISRVEAEDLGVYFCS QSTHIPYTFGGGTKLELKRGGGGSGGGGSGGGGSEVKLVESGGGLVLPGDSLRLSCA TSEFTFTDYYMTWVRQPPRKALEWLGFIRNRANGYTTEYNPSVKGRFTISRDNSQSIL YLQMNTLRTEDSATYYCARVSNWAFDYWGQGTTLTVSS). In some alternatives, the

scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 77. In some alternatives, the scFv is encoded by an ROR1 (R12) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 78 (atgctgctgctggtgacaagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggaacagctcgtcgaaagc ggcggcagactggtgacacctggcggcagcctgaccctgagctgcaaggccagcggcttcgacttcagcgcctactacatgagctg ggtccgccaggcccctggcaagggactggaatggatcgccaccatctaccccagcagcggcaagacctactacgccacctgggtg aacggacggttcaccatctccagcgacaacgcccagaacaccgtggacctgcagatgaacagcctgacagccgccgaccgggcc acctacttttgcgccagagacagctacgccgacgacggcgccctgttcaacatctggggccctggcaccctggtgacaatctctagc ggcggaggcggatctggtggcggaggaagtggcggcggaggatctgagctggtgctgacccagagcccctctgtgtctgctgccc tgggaagccctgccaagatcacctgtaccctgagcagcgcccacaagaccgacaccatcgactggtatcagcagctgcagggcga ggcccccagatacctgatgcaggtgcagagcgacggcagctacaccaagaggccaggcgtgcccgaccggttcagcggatctag ctctggcgccgaccgctacctgatcatccccagcgtgcaggccgatgacgaggccgattactactgtggcgccgactacatcggcg gctacgtgttcggcggaggcacccagctgaccgtgaccggc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 79 (ROR1 (R12) scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQEQLVESGGRLVTPGGSLTLSCKASGFDFSAYYMSW VRQAPGKGLEWIATIYPSSGKTYYATWVNGRFTISSDNAQNTVDLQMNSLTAADRA TYFCARDSYADDGALFNIWGPGTLVTISSGGGGSGGGGSGGGGSELVLTQSPSVSAA LGSPAKITCTLSSAHKTDTIDWYQQLQGEAPRYLMQVQSDGSYTKRPGVPDRFSGSS SGADRYLIIPSVQADDEADYYCGADYIGGYVFGGGTQLTVTG). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 79. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 80 (CD33 (h2H12) VhVl scFv nucleotide sequence

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggttcagctggtgcagtctgga gctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggttacacctttaccaattatgatataaattgggtgag acaggcccctggacaagggcttgagtggattggatggatttatcctggagatggtagtaccaaatataatgagaaattcaaggccaag gctaccctgacagctgacacatccaccagcacagcctacatggagctgaggagcctgagatctgatgacacagctgtgtattactgtg cttctggatatgaagatgctatggactactgggggcaagggaccacagtcacagtctcctca). In some alternatives, the scFv is specific for CD33. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 81 (CD33 (h2H12) VhVl scFv amino acid sequence;

MLLLVTSLLLCELPHPAFLLIPQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYDIN WVRQAPGQGLEWIGWIYPGDGSTKYNEKFKAKATLTADTSTSTAYMELRSLRSDDT AVYYCASGYEDAMDYWGQGTTVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 81. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 82 (CD33 (h2H12) VlVh scFv nucleotide sequence: atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagacatccagatgacccagtctccat cctcactgtctgcatctgtaggagacagagtcaccatcaattgtaaggctagtcaggacattaatagctatttgagctggtttcagcaga aaccagggaaagcccctaagaccctgatctatagagcaaatagattggtagatggggtcccatcaaggttctctggcagtggatctgg gcaagattatactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgcttgcagtatgatgagtttcctctcacatttgg aggagggaccaaggtggagatcaaa). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 83 (CD33 (h2H12) VlVh scFv amino acid sequence: MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTINCKASQDINSYLSWFQ QKPGKAPKTLIYRANRLVDGVPSRFSGSGSGQDYTLTISSLQPEDFATYYCLQYDEFP LTFGGGTKVEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 83. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 84. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 86. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 87. In some alternatives, the spacer is encoded by the nucleic acid sequence set forth in SEQ ID NO: 102 (IgG4 hinge nucleotide sequence: gagagcaagtacggaccgccctgccccccttgccct). In some alternatives, the spacer comprises an amino acid sequence set forth in SEQ ID NO: 103 (IgG4 hinge amino acid sequence: ESKYGPPCPPCP). In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 103. In some alternatives, the spacer is encoded by a nucleic acid sequence set forth in SEQ ID NO: 104. In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range

defined by any two aforementioned values. In some alternatives, HEA3 comprises two amino acid mutations, wherein the sequence is encoded by a sequence set forth in SEQ ID NO: 122 (atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagc gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc atggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc ctgagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct gctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt ggagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcat catgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagc gtgcccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttcccca gcggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccat ggtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacct acccaggccgggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaata gcaccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcc ccacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccag

caccagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttca gcgccctgctgtcccagatcagcagc). In some alternatives, the HEA3 comprises an amino acid sequence set forth in SEQ ID NO: 121 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM DFSALLSQISS). This sequence comprises the sequence of HEA3 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA3(p65/S536E/K310Q). K310Q in RelA corresponds to position 621 in HEA3; S536E corresponds to position 846 in HEA3. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells is provided. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis. In some alternatives, genes that inhibit apoptosis include, for example, Bcl2, and/or CA-Akt. In some alternatives, the polypeptide is Bcl2 or CA-Akt. In some alternatives, genes that inhibit apoptosis include, for example, Survivin, Bcl2, CA-Akt, and/or dnCaspase3. In some alternatives, the polypeptide is Survivin, Bcl2, or CA-Akt and/or dnCaspase 3. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt

cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK ETNNKKKEFEETVKKVRRAIEQLAAMD).

[0302] In some alternatives, a host cell, such as a mammalian cell, comprising a system of any one of the alternatives herein is provided. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral specific molecule, and other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives, the system is for inducible expression of a transgene in cells, such as mammalian cells. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a transgene and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug

that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3.In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the drug is tamoxifen and/or its

metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system, the second promoter is an inducible promoter. In some alternatives of the system, the second promoter is a constitutive promoter. In some alternatives of the system, the second promoter is the EF1αp. In some alternatives of the system, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system, the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system, selectable marker is EGFRt and/or HER2t. In some alternatives of the system, the selectable marker confers drug resistance. In some alternatives of the system, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system, the self-cleaving

peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one

mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the

system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the second nucleic acid further comprises: a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the system, the first promoter is in opposite orientation to the second promoter. In some alternatives of the system, the ligand binding domain is an antibody fragment. In some alternatives of the system, the ligand binding domain is a single chain variable fragment. In some alternatives of the system, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof. In some alternatives of the system, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the system, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC or VAR2CSA. In some alternatives of the system, the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or

80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the host cell is a precursor T cell. In some alternatives, the precursor T cell is a hematopoietic stem cell. In some alternatives, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the chimeric antigen receptor comprises a scFv. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv comprises an huCD19 scFv (G01S) amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 41 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMH WVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDT AVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQ PRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSR SGRAASLIISGLQTEDEADYFCSSYAGRYNSVLFGGGTKLTVL). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 41. In some alternatives, the scFv is encoded by the muCD19 (FMC63) scFv nucleotide sequence. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 42 (Atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccgacatccagatgacccagac cacctccagcctgagcgccagcctgggcgaccgggtgaccatcagctgccgggccagccaggacatcagcaagtacctgaactg gtatcagcagaagcccgacggcaccgtcaagctgctgatctaccacaccagccggctgcacagcggcgtgcccagccggtttagc ggcagcggctccggcaccgactacagcctgaccatctccaacctggaacaggaagatatcgccacctacttttgccagcagggcaa cacactgccctacacctttggcggcggaacaaagctggaaatcaccggcagcacctccggcagcggcaagcctggcagcggcga

gggcagcaccaagggcgaggtgaagctgcaggaaagcggccctggcctggtggcccccagccagagcctgagcgtgacctgca ccgtgagcggcgtgagcctgcccgactacggcgtgagctggatccggcagcccccaggaagggcctggaatggctgggcgtga tctggggcagcgagaccacctactacaacagcgccctgaagagccggctgaccatcatcaaggacaacagcaagagccaggtgtt cctgaagatgaacagcctgcagaccgacgacaccgccatctactactgcgccaagcactactactacggcggcagctacgccatgg actactggggccagggcaccagcgtgaccgtgagcagc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 43 (MLLLVTSLLLCELPHPAFLLIPDIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWY QQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLP YTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVSGVS LPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSL QTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 43. some alternatives, the scFv comprises a B7H3 (hBRCA84D) scFv nucleotide sequence. In some alternatives, the scFv binds specifically to the B7-H3 receptor. In some alternatives, the scFv comprises the L1CAM (CE7) scFv nucleotide sequence. In some alternatives, the scFv is specific for the epitope, CE7 epitope, of L1CAM. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 50

(atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccaggtgcagctgcagcagcct ggcgccgagctggtgaagccaggcgccagcgtgaagctgtcctgcaaggccagcggctacaccttcaccggctactggatgcact gggtgaagcagagacccggccacggcctggaatggatcggcgagatcaaccccagcaacggccggaccaactacaacgagcgg ttcaagagcaaggccaccctgaccgtggacaagagcagcaccaccgccttcatgcagctgtccggcctgaccagcgaggacagcg ccgtgtacttctgcgccagggactactacggcaccagctacaacttcgactactggggccagggcaccacactgaccgtgagcagc ggcggaggggggctctggcggcggaggatctgggggaggggggcagcgacatccagatgacccagagcagcagcagcttcagcg tgagcctgggcgaccgggtgaccatcacctgtaaggccaacgaggacatcaacaaccggctggcctggtatcagcagacccccgg caacagccccaggctgctgatcagcggcgccaccaacctggtgaccggcgtgcccagccggtttagcggcagcggctccggcaa ggactacaccctgaccatcacaagcctgcaggccgaggacttcgccacctactactgccagcagtactggtccacccccttcaccttc ggcagcggcaccgagctggaaatcaaa). In some alternatives, the scFv comprises the L1CAM (CE7) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 51 (MLLLVTSLLLCELPHPAFLLIPQVQLQQPGAELVKPGASVKLSCKASGYTFTGYWM

HWVKQRPGHGLEWIGEINPSNGRTNYNERFKSKATLTVDKSSTTAFMQLSGLTSEDS
AVYFCARDYYGTSYNFDYWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSSSSFS
VSLGDRVTITCKANEDINNRLAWYQQTPGNSPRLLISGATNLVTGVPSRFSGSGSGK
DYTLTITSLQAEDFATYYCQQYWSTPFTFGSGTELEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 51. In some alternatives, the scFv is encoded by the EGFR (cetuximab) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 52 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtgcagctgaaacagagcg
gcccgggcctggtgcagccgagccagagcctgagcattacctgcaccgtgagcggctttagcctgaccaactatggcgtgcattgg
gtgcgccagagcccgggcaaaggcctggaatggctgggcgtgatttggagcggcggcaacaccgattataacaccccgtttacca
gccgcctgagcattaacaaagataacagcaaaagccaggtgtttttttaaaatgaacagcctgcagagcaacgataccgcgatttattat
tgcgcgcgcgcgctgacctattatgattatgaatttgcgtattggggccagggcaccctggtgaccgtgagcgcgggcggcggcgg
cagcggcggcggcggcagcggcggcggcggcagcgatattctgctgacccagagcccggtgattctgagcgtgagcccgggcg
aacgcgtgagctttagctgccgcgcgagccagagcattggcaccaacattcattggtatcagcagcgcaccaacggcagcccgcgc
ctgctgattaaatatgcgagcgaaagcattagcggcattccgagccgctttagcggcagcggcagcggcaccgattttaccctgagc
attaacagcgtggaaagcgaagatattgcggattattattgccagcagaacaacaactggccgaccacctttggcgcgggcaccaaa
ctggaactgaaacgcacc). In some alternatives, the scFv comprises the EGFR scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 53 (MLLLVTSLLLCELPHPAFLLIPQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHW
VRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIY
YCARALTYYDYEFAYWGQGTLVTVSAGGGGSGGGGSGGGGSDILLTQSPVILSVSP
GERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSI
NSVESEDIADYYCQQNNNWPTTFGAGTKLELKRT). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 53. In some alternatives, the scFv comprises the EGFRVIII (806) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by the EphA2 (2A4) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 56. In

some alternatives, the scFv is encoded by the EpHA2 (4H5) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 58. In some alternatives, the scFv is encoded by a FITC (E2) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 60. In some alternatives, the scFv is encoded by an IL13Ra2 (hu08) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 68. In some alternatives, the scFv comprises an IL13Ra2 hu08 VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 69 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFSRNGMS WVRQAPGKGLEWVATVSSGGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARQGTTALATRFFDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSS LSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIYSASYRSTGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQHHYSAPWTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 69. In some alternatives, the scFv is encoded by an IL13Ra2 (hu07) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 70 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatattcagatgacccagagccc gagcagcctgagcgcgagcgtgggcgatcgcgtgaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggt atcagcagaaaccgggcaaagcgccgaaactgctgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcgg cagcggcagcggcaccgattttaccctgaccattagcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgca gcccgctgacctttggcggcggcaccaaagtggaaattaaaggtggtggttctggcggcggcggctccggtggtggtggttctg aagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacct ttaccaaatatggcgtgcattgggtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagca ccgattataacagcgcgctgatgagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgc gcgcggaagataccgcggtgtattattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtg agcagcgaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 71 (MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCTASLSVSSTYLHWY

QQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCHQYHRSP
LTFGGGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFT
KYGVHWVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNS
LRAEDTAVYYCARDHRDAMDYWGQGTLVTVSSESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 71. In some alternatives, the scFv is encoded by the IL13Ra2 (hu07) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 72 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagaagtgcagctggtggaaagcg gcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacctttaccaaatatggcgtgcattgg gtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagcaccgattataacagcgcgctgat gagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgcgcgcggaagataccgcggtgt attattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtgagcagcggtggtggtggttctg gcggcggcggctccggtggtggtggttctgatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatcgcgt gaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggtatcagcagaaaccgggcaaagcgccgaaactgc tgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcggcagcggcagcggcaccgattttaccctgaccatta gcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgcagcccgctgacctttggcggcggcaccaaagtgga aattaaagaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 73 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFTKYGVH WVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNSLRAED TAVYYCARDHRDAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCTASLSVSSTYLHWYQQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCHQYHRSPLTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 73. In some alternatives, the antibody or portion thereof or scFv is encoded by the Anti-IL13Ra2 (IL13 zetakine) nucleotide sequence. In some alternatives, the antibody or portion thereof or scFv is encoded by a sequence set forth in SEQ ID NO: 74 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaggccctgtgcctccctctacagcc

ctcaggtacctcattgaggagctggtcaacatcacccagaaccagaaggctccgctctgcaatggcagcatggtatggagcatcaac ctgacagctggcatgtactgtgcagccctggaatccctgatcaacgtgtcaggctgcagtgccatcgagaagacccagaggatgctg agcggattctgcccgcacaaggtctcagctgggcagttttccagcttgcatgtccgagacaccaaaatcgaggtggcccagtttgtaa aggacctgctcttacatttaaagaaacttttcgcgagggacggttcaa). In some alternatives, the antibody or portion thereof or scFv comprises an Anti-IL13Ra2 (IL13 zetakine) amino acid sequence. In some alternatives, the antibody or portion thereof or scFv comprises an amino acid sequence set forth in SEQ ID NO: 75 (MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSI NLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQ FVKDLLLHLKKLFREGRF). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 75. In some alternatives, the scFv is encoded by an oaGD2 (8B6) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 76

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatgttgtgatgacccaaactcca ctctccctgcctgtcagtcttggagatcaagcctcaatctcttgcagatctagtcagagccttctaaaaaataatggaaacacctttttaca ttggtacctgcagaagtcaggccagtctccaaagctccttatctacaaagtttccaaccgactttctggggtcccagacaggttcagtgg cagtggatcagggacatatttcacactcaagatcagcagagtggaggctgaggatctgggagtttatttctgctctcaaagtacacatat tccgtacacattcggaggggggaccaagctcgagctgaaacgaggcggaggggctctggcggcggaggatctgggggagggg gcagcgaggtgaaactggtggagtctggaggaggcttggtgctgcctggggattctctgagactctcctgtgcaacttctgagttcac cttcactgattactacatgacttgggtccgccagcctccaagaaaggcacttgagtggttgggttttattagaaacagagctaatggttac acaacagagtacaatccatctgtgaagggtcggttcaccatttccagagataattcccaaagcatcctctatcttcaaatgaacaccctg agaactgaggacagtgccacttattactgtgcaagagtctctaactgggcctttgactactggggccaaggcaccactctcacagtctc ctca). In some alternatives, the scFv comprises the oaGD2 (8B6) VlVh scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 77 (MLLLVTSLLLCELPHPAFLLIPDVVMTQTPLSLPVSLGDQASISCRSSQSLLKNNGNT FLHWYLQKSGQSPKLLIYKVSNRLSGVPDRFSGSGSGTYFTLKISRVEAEDLGVYFCS QSTHIPYTFGGGTKLELKRGGGGSGGGGSGGGGSEVKLVESGGGLVLPGDSLRLSCA TSEFTFTDYYMTWVRQPPRKALEWLGFIRNRANGYTTEYNPSVKGRFTISRDNSQSIL YLQMNTLRTEDSATYYCARVSNWAFDYWGQGTTLTVSS). In some alternatives, the

scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 77. In some alternatives, the scFv is encoded by an ROR1 (R12) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 78 (atgctgctgctggtgacaagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggaacagctcgtcgaaagc ggcggcagactggtgacacctggcggcagcctgaccctgagctgcaaggccagcggcttcgacttcagcgcctactacatgagctg ggtccgccaggcccctggcaagggactggaatggatcgccaccatctaccccagcagcggcaagacctactacgccacctgggtg aacggacggttcaccatctccagcgacaacgcccagaacaccgtggacctgcagatgaacagcctgacagccgccgaccgggcc acctacttttgcgccagagacagctacgccgacgacggcgccctgttcaacatctggggccctggcaccctggtgacaatctctagc ggcggaggcggatctggtggcggaggaagtggcggcggaggatctgagctggtgctgacccagagcccctctgtgtctgctgccc tgggaagccctgccaagatcacctgtaccctgagcagcgcccacaagaccgacaccatcgactggtatcagcagctgcagggcga ggcccccagatacctgatgcaggtgcagagcgacggcagctacaccaagaggccaggcgtgcccgaccggttcagcggatctag ctctggcgccgaccgctacctgatcatccccagcgtgcaggccgatgacgaggccgattactactgtggcgccgactacatcggcg gctacgtgttcggcggaggcacccagctgaccgtgaccggc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 79 (ROR1 (R12) scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQEQLVESGGRLVTPGGSLTLSCKASGFDFSAYYMSW VRQAPGKGLEWIATIYPSSGKTYYATWVNGRFTISSDNAQNTVDLQMNSLTAADRA TYFCARDSYADDGALFNIWGPGTLVTISSGGGGSGGGGSGGGGSELVLTQSPSVSAA LGSPAKITCTLSSAHKTDTIDWYQQLQGEAPRYLMQVQSDGSYTKRPGVPDRFSGSS SGADRYLIIPSVQADDEADYYCGADYIGGYVFGGGTQLTVTG). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 79. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 80 (CD33 (h2H12) VhVl scFv nucleotide sequence

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggttcagctggtgcagtctgga gctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggttacacctttaccaattatgatataaattgggtgag acaggcccctggacaagggcttgagtggattggatggatttatcctggagatggtagtaccaaatataatgagaaattcaaggccaag gctaccctgacagctgacacatccaccagcacagcctacatggagctgaggagcctgagatctgatgacacagctgtgtattactgtg cttctggatatgaagatgctatggactactgggggcaagggaccacagtcacagtctcctca). In some alternatives, the scFv is specific for CD33. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 81 (CD33 (h2H12) VhVl scFv amino acid sequence;

MLLLVTSLLLCELPHPAFLLIPQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYDIN WVRQAPGQGLEWIGWIYPGDGSTKYNEKFKAKATLTADTSTSTAYMELRSLRSDDT AVYYCASGYEDAMDYWGQGTTVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 81. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 82 (CD33 (h2H12) VlVh scFv nucleotide sequence: atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagacatccagatgacccagtctccat cctcactgtctgcatctgtaggagacagagtcaccatcaattgtaaggctagtcaggacattaatagctatttgagctggtttcagcaga aaccagggaaagcccctaagaccctgatctatagagcaaatagattggtagatggggtcccatcaaggttctctggcagtggatctgg gcaagattatactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgcttgcagtatgatgagtttcctctcacatttgg aggagggaccaaggtggagatcaaa). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 83 (CD33 (h2H12) VlVh scFv amino acid sequence: MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTINCKASQDINSYLSWFQ QKPGKAPKTLIYRANRLVDGVPSRFSGSGSGQDYTLTISSLQPEDFATYYCLQYDEFP LTFGGGTKVEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 83. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 84. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 86. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 87. In some alternatives, the spacer is encoded by the nucleic acid sequence set forth in SEQ ID NO: 102 (IgG4 hinge nucleotide sequence: gagagcaagtacggaccgccctgccccccttgccct). In some alternatives, the spacer comprises an amino acid sequence set forth in SEQ ID NO: 103 (IgG4 hinge amino acid sequence: ESKYGPPCPPCP). In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 103. In some alternatives, the spacer is encoded by a nucleic acid sequence set forth in SEQ ID NO: 104. In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range

defined by any two aforementioned values. In some alternatives, HEA3 comprises two amino acid mutations, wherein the sequence is encoded by a sequence set forth in SEQ ID NO: 122 (atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagc gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc atggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc ctgagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct gctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt ggagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcat catgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagc gtgcccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttcccca gcggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccat ggtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacct acccaggccgggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaata gcaccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcc ccacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccag

caccagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttca gcgccctgctgtcccagatcagcagc). In some alternatives, the HEA3 comprises an amino acid sequence set forth in SEQ ID NO: 121 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM DFSALLSQISS). This sequence comprises the sequence of HEA3 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA3(p65/S536E/K310Q). K310Q in RelA corresponds to position 621 in HEA3; S536E corresponds to position 846 in HEA3. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells is provided. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis. In some alternatives, genes that inhibit apoptosis include, for example, Bcl2, and/or CA-Akt. In some alternatives, the polypeptide is Bcl2 or CA-Akt. In some alternatives, genes that inhibit apoptosis include, for example, Survivin, Bcl2, CA-Akt, and/or dnCaspase3. In some alternatives, the polypeptide is Survivin, Bcl2, or CA-Akt and/or dnCaspase 3. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt

cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK ETNNKKKEFEETVKKVRRAIEQLAAMD).

[0303] In some alternatives, a composition comprising a host cell, such as a mammalian cell, of any one or more of the alternatives herein is provided, in a pharmaceutically acceptable excipient. In some alternatives, the host cell, such as a mammalian cell, comprises a system of any one of the alternatives herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells,. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral molecule, and other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an

estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM

drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system, the second promoter is an inducible promoter. In some alternatives of the system, the second promoter is a constitutive promoter. In some alternatives of the system, the second promoter is the EF1αp. In some alternatives of the system, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system, the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system, selectable marker is EGFRt and/or HER2t. In some alternatives of the system, the selectable marker confers drug resistance. In some alternatives of the system, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID

NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-

LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the second nucleic acid further comprises: a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target

cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optionally optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the system, the first promoter is in opposite orientation to the second promoter. In some alternatives of the system, the ligand binding domain is an antibody fragment, such as a binding fragment. In some alternatives of the system, the ligand binding domain is a single chain variable fragment. In some alternatives of the system, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof. In some alternatives of the system, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the system, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC or VAR2CSA. In some alternatives of the system, the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the host cell is a precursor T cell. In some alternatives, the precursor T cell is a hematopoietic stem cell. In

some alternatives, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the composition comprises a host cell, wherein the host cell is a precursor T cell and a host cell wherein the host cell is a hematopoietic stem cell. In some alternatives, the composition comprises a host cell, wherein the host cell is a precursor T cell or a hematopoietic stem cell and a host cell that is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells or a CD4+ T cell selected from naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the chimeric antigen receptor comprises a scFv. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv comprises an huCD19 scFv (G01S) amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 41 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMH WVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDT AVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQ PRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSR SGRAASLIISGLQTEDEADYFCSSYAGRYNSVLFGGGTKLTVL). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 41. In some alternatives, the scFv is encoded by the muCD19 (FMC63) scFv nucleotide sequence. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 42 (Atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccgacatccagatgacccagac cacctccagcctgagcgccagcctgggcgaccgggtgaccatcagctgccgggccagccaggacatcagcaagtacctgaactg gtatcagcagaagcccgacggcaccgtcaagctgctgatctaccacaccagccggctgcacagcggcgtgcccagccggtttagc ggcagcggctccggcaccgactacagcctgaccatctccaacctggaacaggaagatatcgccacctacttttgccagcagggcaa cacactgccctacacctttggcggcggaacaaagctggaaatcaccggcagcacctccggcagcggcaagcctggcagcggcga

gggcagcaccaagggcgaggtgaagctgcaggaaagcggccctggcctggtggcccccagccagagcctgagcgtgacctgca ccgtgagcggcgtgagcctgcccgactacggcgtgagctggatccggcagcccccaggaagggcctggaatggctgggcgtga tctggggcagcgagaccacctactacaacagcgccctgaagagccggctgaccatcatcaaggacaacagcaagagccaggtgtt cctgaagatgaacagcctgcagaccgacgacaccgccatctactactgcgccaagcactactactacggcggcagctacgccatgg actactggggccagggcaccagcgtgaccgtgagcagc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 43 (MLLLVTSLLLCELPHPAFLLIPDIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWY QQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLP YTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVSGVS LPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSL QTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 43. some alternatives, the scFv comprises a B7H3 (hBRCA84D) scFv nucleotide sequence. In some alternatives, the scFv binds specifically to the B7-H3 receptor. In some alternatives, the scFv comprises the L1CAM (CE7) scFv nucleotide sequence. In some alternatives, the scFv is specific for the epitope, CE7 epitope, of L1CAM. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 50

(atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccaggtgcagctgcagcagcct ggcgccgagctggtgaagccaggcgccagcgtgaagctgtcctgcaaggccagcggctacaccttcaccggctactggatgcact gggtgaagcagagacccggccacggcctggaatggatcggcgagatcaaccccagcaacggccggaccaactacaacgagcgg ttcaagagcaaggccaccctgaccgtggacaagagcagcaccaccgccttcatgcagctgtccggcctgaccagcgaggacagcg ccgtgtacttctgcgccagggactactacggcaccagctacaacttcgactactggggccagggcaccacactgaccgtgagcagc ggcggaggggggctctggcggcggaggatctgggggaggggggcagcgacatccagatgacccagagcagcagcagcttcagcg tgagcctgggcgaccgggtgaccatcacctgtaaggccaacgaggacatcaacaaccggctggcctggtatcagcagacccccgg caacagccccaggctgctgatcagcggcgccaccaacctggtgaccggcgtgcccagccggtttagcggcagcggctccggcaa ggactacaccctgaccatcacaagcctgcaggccgaggacttcgccacctactactgccagcagtactggtccacccccttcaccttc ggcagcggcaccgagctggaaatcaaa). In some alternatives, the scFv comprises the L1CAM (CE7) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 51 (MLLLVTSLLLCELPHPAFLLIPQVQLQQPGAELVKPGASVKLSCKASGYTFTGYWM

HWVKQRPGHGLEWIGEINPSNGRTNYNERFKSKATLTVDKSSTTAFMQLSGLTSEDS
AVYFCARDYYGTSYNFDYWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSSSSFS
VSLGDRVTITCKANEDINNRLAWYQQTPGNSPRLLISGATNLVTGVPSRFSGSGSGK
DYTLTITSLQAEDFATYYCQQYWSTPFTFGSGTELEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 51. In some alternatives, the scFv is encoded by the EGFR (cetuximab) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 52 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtgcagctgaaacagagcg
gcccgggcctggtgcagccgagccagagcctgagcattacctgcaccgtgagcggctttagcctgaccaactatggcgtgcattgg
gtgcgccagagcccgggcaaaggcctggaatggctgggcgtgatttggagcggcggcaacaccgattataacaccccgtttacca
gccgcctgagcattaacaaagataacagcaaaagccaggtgtttttttaaaatgaacagcctgcagagcaacgataccgcgatttattat
tgcgcgcgcgcgctgacctattatgattatgaatttgcgtattggggccagggcaccctggtgaccgtgagcgcgggcggcggcgg
cagcggcggcggcggcagcggcggcggcggcagcgatattctgctgacccagagcccggtgattctgagcgtgagcccgggcg
aacgcgtgagctttagctgccgcgcgagccagagcattggcaccaacattcattggtatcagcagcgcaccaacggcagcccgcgc
ctgctgattaaatatgcgagcgaaagcattagcggcattccgagccgctttagcggcagcggcagcggcaccgattttaccctgagc
attaacagcgtggaaagcgaagatattgcggattattattgccagcagaacaacaactggccgaccacctttggcgcgggcaccaaa
ctggaactgaaacgcacc). In some alternatives, the scFv comprises the EGFR scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 53 (MLLLVTSLLLCELPHPAFLLIPQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHW
VRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIY
YCARALTYYDYEFAYWGQGTLVTVSAGGGGSGGGGSGGGGSDILLTQSPVILSVSP
GERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSI
NSVESEDIADYYCQQNNNWPTTFGAGTKLELKRT). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 53. In some alternatives, the scFv comprises the EGFRVIII (806) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by the EphA2 (2A4) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 56. In

some alternatives, the scFv is encoded by the EpHA2 (4H5) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 58. In some alternatives, the scFv is encoded by a FITC (E2) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 60. In some alternatives, the scFv is encoded by an IL13Ra2 (hu08) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 68. In some alternatives, the scFv comprises an IL13Ra2 hu08 VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 69 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFSRNGMS WVRQAPGKGLEWVATVSSGGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARQGTTALATRFFDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSS LSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIYSASYRSTGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQHHYSAPWTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 69. In some alternatives, the scFv is encoded by an IL13Ra2 (hu07) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 70 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatattcagatgacccagagccc gagcagcctgagcgcgagcgtgggcgatcgcgtgaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggt atcagcagaaaccgggcaaagcgccgaaactgctgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcgg cagcggcagcggcaccgattttaccctgaccattagcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgca gcccgctgacctttggcggcggcaccaaagtggaaattaaaggtggtggtggttctggcggcggcggctccggtggtggtggttctg aagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacct ttaccaaatatggcgtgcattgggtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagca ccgattataacagcgcgctgatgagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgc gcgcggaagataccgcggtgtattattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtg agcagcgaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 71 (MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCTASLSVSSTYLHWY

QQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCHQYHRSP
LTFGGGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFT
KYGVHWVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNS
LRAEDTAVYYCARDHRDAMDYWGQGTLVTVSSESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 71. In some alternatives, the scFv is encoded by the IL13Ra2 (hu07) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 72 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagaagtgcagctggtggaaagcg gcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacctttaccaaatatggcgtgcattgg gtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagcaccgattataacagcgcgctgat gagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgcgcgcggaagataccgcggtgt attattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtgagcagcggtggtggtggttctg gcggcggcggctccggtggtggtggttctgatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatcgcgt gaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggtatcagcagaaaccgggcaaagcgccgaaactgc tgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcggcagcggcagcggcaccgattttaccctgaccatta gcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgcagcccgctgacctttggcggcggcaccaaagtgga aattaaagaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 73 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFTKYGVH WVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNSLRAED TAVYYCARDHRDAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCTASLSVSSTYLHWYQQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCHQYHRSPLTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 73. In some alternatives, the antibody or portion thereof or scFv is encoded by the Anti-IL13Ra2 (IL13 zetakine) nucleotide sequence. In some alternatives, the antibody or portion thereof or scFv is encoded by a sequence set forth in SEQ ID NO: 74 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaggccctgtgcctccctctacagcc

ctcaggtacctcattgaggagctggtcaacatcacccagaaccagaaggctccgctctgcaatggcagcatggtatggagcatcaac ctgacagctggcatgtactgtgcagccctggaatccctgatcaacgtgtcaggctgcagtgccatcgagaagacccagaggatgctg agcggattctgcccgcacaaggtctcagctgggcagttttccagcttgcatgtccgagacaccaaaatcgaggtggcccagtttgtaa aggacctgctcttacatttaaagaaacttttcgcgagggacggttcaa). In some alternatives, the antibody or portion thereof or scFv comprises an Anti-IL13Ra2 (IL13 zetakine) amino acid sequence. In some alternatives, the antibody or portion thereof or scFv comprises an amino acid sequence set forth in SEQ ID NO: 75 (MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSI NLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQ FVKDLLLHLKKLFREGRF). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 75. In some alternatives, the scFv is encoded by an oaGD2 (8B6) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 76

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatgttgtgatgacccaaactcca ctctccctgcctgtcagtcttggagatcaagcctcaatctcttgcagatctagtcagagccttctaaaaaataatggaaacacctttttaca ttggtacctgcagaagtcaggccagtctccaaagctccttatctacaaagtttccaaccgactttctggggtcccagacaggttcagtgg cagtggatcagggacatatttcacactcaagatcagcagagtggaggctgaggatctgggagtttatttctgctctcaaagtacacatat tccgtacacattcggaggggggaccaagctcgagctgaaacgaggcggaggggctctggcggcggaggatctgggggagggg gcagcgaggtgaaactggtggagtctggaggaggcttggtgctgcctggggattctctgagactctcctgtgcaacttctgagttcac cttcactgattactacatgacttgggtccgccagcctccaagaaaggcacttgagtggttgggttttattagaaacagagctaatggttac acaacagagtacaatccatctgtgaagggtcggttcaccatttccagagataattcccaaagcatcctctatcttcaaatgaacaccctg agaactgaggacagtgccacttattactgtgcaagagtctctaactgggcctttgactactggggccaaggcaccactctcacagtctc ctca). In some alternatives, the scFv comprises the oaGD2 (8B6) VlVh scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 77 (MLLLVTSLLLCELPHPAFLLIPDVVMTQTPLSLPVSLGDQASISCRSSQSLLKNNGNT FLHWYLQKSGQSPKLLIYKVSNRLSGVPDRFSGSGSGTYFTLKISRVEAEDLGVYFCS QSTHIPYTFGGGTKLELKRGGGGSGGGGSGGGGSEVKLVESGGGLVLPGDSLRLSCA TSEFTFTDYYMTWVRQPPRKALEWLGFIRNRANGYTTEYNPSVKGRFTISRDNSQSIL YLQMNTLRTEDSATYYCARVSNWAFDYWGQGTTLTVSS). In some alternatives, the

scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 77. In some alternatives, the scFv is encoded by an ROR1 (R12) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 78 (atgctgctgctggtgacaagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggaacagctcgtcgaaagc ggcggcagactggtgacacctggcggcagcctgaccctgagctgcaaggccagcggcttcgacttcagcgcctactacatgagctg ggtccgccaggcccctggcaagggactggaatggatcgccaccatctaccccagcagcggcaagacctactacgccacctgggtg aacggacggttcaccatctccagcgacaacgcccagaacaccgtggacctgcagatgaacagcctgacagccgccgaccgggcc acctacttttgcgccagagacagctacgccgacgacggcgccctgttcaacatctggggccctggcaccctggtgacaatctctagc ggcggaggcggatctggtggcggaggaagtggcggcggaggatctgagctggtgctgacccagagcccctctgtgtctgctgccc tgggaagccctgccaagatcacctgtaccctgagcagcgcccacaagaccgacaccatcgactggtatcagcagctgcagggcga ggcccccagatacctgatgcaggtgcagagcgacggcagctacaccaagaggccaggcgtgcccgaccggttcagcggatctag ctctggcgccgaccgctacctgatcatccccagcgtgcaggccgatgacgaggccgattactactgtggcgccgactacatcggcg gctacgtgttcggcggaggcacccagctgaccgtgaccggc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 79 (ROR1 (R12) scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQEQLVESGGRLVTPGGSLTLSCKASGFDFSAYYMSW VRQAPGKGLEWIATIYPSSGKTYYATWVNGRFTISSDNAQNTVDLQMNSLTAADRA TYFCARDSYADDGALFNIWGPGTLVTISSGGGGSGGGGSGGGGSELVLTQSPSVSAA LGSPAKITCTLSSAHKTDTIDWYQQLQGEAPRYLMQVQSDGSYTKRPGVPDRFSGSS SGADRYLIIPSVQADDEADYYCGADYIGGYVFGGGTQLTVTG). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 79. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 80 (CD33 (h2H12) VhVl scFv nucleotide sequence

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggttcagctggtgcagtctgga gctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggttacacctttaccaattatgatataaattgggtgag acaggcccctggacaagggcttgagtggattggatggatttatcctggagatggtagtaccaaatataatgagaaattcaaggccaag gctaccctgacagctgacacatccaccagcacagcctacatggagctgaggagcctgagatctgatgacacagctgtgtattactgtg cttctggatatgaagatgctatggactactgggggcaagggaccacagtcacagtctcctca). In some alternatives, the scFv is specific for CD33. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 81 (CD33 (h2H12) VhVl scFv amino acid sequence;

MLLLVTSLLLCELPHPAFLLIPQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYDIN WVRQAPGQGLEWIGWIYPGDGSTKYNEKFKAKATLTADTSTSTAYMELRSLRSDDT AVYYCASGYEDAMDYWGQGTTVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 81. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 82 (CD33 (h2H12) VlVh scFv nucleotide sequence: atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagacatccagatgacccagtctccat cctcactgtctgcatctgtaggagacagagtcaccatcaattgtaaggctagtcaggacattaatagctatttgagctggtttcagcaga aaccagggaaagcccctaagaccctgatctatagagcaaatagattggtagatggggtcccatcaaggttctctggcagtggatctgg gcaagattatactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgcttgcagtatgatgagtttcctctcacatttgg aggagggaccaaggtggagatcaaa). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 83 (CD33 (h2H12) VlVh scFv amino acid sequence: MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTINCKASQDINSYLSWFQ QKPGKAPKTLIYRANRLVDGVPSRFSGSGSGQDYTLTISSLQPEDFATYYCLQYDEFP LTFGGGTKVEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 83. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 84. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 86. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 87. In some alternatives, the spacer is encoded by the nucleic acid sequence set forth in SEQ ID NO: 102 (IgG4 hinge nucleotide sequence: gagagcaagtacggaccgccctgccccccttgccct). In some alternatives, the spacer comprises an amino acid sequence set forth in SEQ ID NO: 103 (IgG4 hinge amino acid sequence: ESKYGPPCPPCP). In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 103. In some alternatives, the spacer is encoded by a nucleic acid sequence set forth in SEQ ID NO: 104. In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range

defined by any two aforementioned values. In some alternatives, HEA3 comprises two amino acid mutations, wherein the sequence is encoded by a sequence set forth in SEQ ID NO: 122 (atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagc gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc atggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc ctgagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct gctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt ggagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcat catgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagc gtgcccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttcccca gcggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccat ggtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacct acccaggccgggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaata gcaccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcc ccacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccag

caccagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttca gcgccctgctgtcccagatcagcagc). In some alternatives, the HEA3 comprises an amino acid sequence set forth in SEQ ID NO: 121 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM DFSALLSQISS). This sequence comprises the sequence of HEA3 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA3(p65/S536E/K310Q). K310Q in RelA corresponds to position 621 in HEA3; S536E corresponds to position 846 in HEA3. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells is provided. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis. In some alternatives, genes that inhibit apoptosis include, for example, Bcl2, and/or CA-Akt. In some alternatives, the polypeptide is Bcl2 or CA-Akt. In some alternatives, genes that inhibit apoptosis include, for example, Survivin, Bcl2, CA-Akt, and/or dnCaspase3. In some alternatives, the polypeptide is Survivin, Bcl2, or CA-Akt and/or dnCaspase 3. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt

cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK ETNNKKKEFEETVKKVRRAIEQLAAMD).

[0304] In some alternatives, an *in vitro* method for preparing a host cell of any one of alternatives herein is provided. The method comprises a) providing a system of any one of the alternatives herein; and b) introducing the system into an isolated T lymphocyte population and expanding each T lymphocyte population in vitro. In some alternatives, the T lymphocytes are expanded, and wherein the method further comprises culturing the cells in the presence of anti-CD3 and/or anti CD28, and at least one homeostatic cytokine until the cells expand sufficiently for use as a cell infusion. In some alternatives, the isolated T lymphocyte population comprises precursor T cells. In some alternatives, the precursor T cells are hematopoietic stem cells. In some alternatives, the lymphocyte is CD8+ or CD4+. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral specific molecule, and other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the

system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system, the drug induces a high expression of the

chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system, the second promoter is an inducible promoter. In some alternatives of the system, the second promoter is a constitutive promoter. In some alternatives of the system, the second promoter is the EF1αp. In some alternatives of the system, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system, the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system, selectable marker is EGFRt and/or HER2t. In some alternatives of the system, the selectable marker confers drug resistance. In some alternatives of the system, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives of the

system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least

one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are

cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the second nucleic acid further comprises: a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the system, the first promoter is in opposite orientation to the second promoter. In some alternatives of the system, the ligand binding domain is an antibody fragment. In some alternatives of the system, the ligand binding domain is a single chain variable fragment. In some alternatives of the system, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof. In some alternatives of the system, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the system, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives of the system, the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives

of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the chimeric antigen receptor comprises a scFv. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv comprises an huCD19 scFv (G01S) amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 41 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMH WVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDT AVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQ PRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSR SGRAASLIISGLQTEDEADYFCSSYAGRYNSVLFGGGTKLTVL). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 41. In some alternatives, the scFv is encoded by the muCD19 (FMC63) scFv nucleotide sequence. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 42 (Atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccgacatccagatgacccagac cacctccagcctgagcgccagcctgggcgaccgggtgaccatcagctgccgggccagccaggacatcagcaagtacctgaactg gtatcagcagaagcccgacggcaccgtcaagctgctgatctaccacaccagccggctgcacagcggcgtgcccagccggtttagc ggcagcggctccggcaccgactacagcctgaccatctccaacctggaacaggaagatatcgccacctacttttgccagcagggcaa cacactgccctacacctttggcggcggaacaaagctggaaatcaccggcagcacctccggcagcggcaagcctggcagcggcga gggcagcaccaagggcgaggtgaagctgcaggaaagcggccctggcctggtggcccccagccagagcctgagcgtgacctgca ccgtgagcggcgtgagcctgcccgactacggcgtgagctggatccggcagccccccaggaagggcctggaatggctgggcgtga tctggggcagcgagaccacctactacaacagcgccctgaagagccggctgaccatcatcaaggacaacagcaagagccaggtgtt cctgaagatgaacagcctgcagaccgacgacaccgccatctactactgcgccaagcactactactacggcggcagctacgccatgg actactggggccagggcaccagcgtgaccgtgagcagc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 43 (MLLLVTSLLLCELPHPAFLLIPDIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWY QQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLP YTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVSGVS

LPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSL QTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 43. some alternatives, the scFv comprises a B7H3 (hBRCA84D) scFv nucleotide sequence. In some alternatives, the scFv binds specifically to the B7-H3 receptor. In some alternatives, the scFv comprises the L1CAM (CE7) scFv nucleotide sequence. In some alternatives, the scFv is specific for the epitope, CE7 epitope, of L1CAM. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 50

(atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccaggtgcagctgcagcagcct ggcgccgagctggtgaagccaggcgccagcgtgaagctgtcctgcaaggccagcggctacaccttcaccggctactggatgcact gggtgaagcagagacccggccacggcctggaatggatcggcgagatcaaccccagcaacggccggaccaactacaacgagcgg ttcaagagcaaggccaccctgaccgtggacaagagcagcaccaccgccttcatgcagctgtccggcctgaccagcgaggacagcg ccgtgtacttctgcgccagggactactacggcaccagctacaacttcgactactggggccagggcaccacactgaccgtgagcagc ggcggaggggggctctggcggcggaggatctgggggaggggggcagcgacatccagatgacccagagcagcagcagcttcagcg tgagcctgggcgaccgggtgaccatcacctgtaaggccaacgaggacatcaacaaccggctggcctggtatcagcagacccccgg caacagccccaggctgctgatcagcggcgccaccaacctggtgaccggcgtgcccagccggtttagcggcagcggctccggcaa ggactacaccctgaccatcacaagcctgcaggccgaggacttcgccacctactactgccagcagtactggtccacccccttcaccttc ggcagcggcaccgagctggaaatcaaa). In some alternatives, the scFv comprises the L1CAM (CE7) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 51 (MLLLVTSLLLCELPHPAFLLIPQVQLQQPGAELVKPGASVKLSCKASGYTFTGYWM HWVKQRPGHGLEWIGEINPSNGRTNYNERFKSKATLTVDKSSTTAFMQLSGLTSEDS AVYFCARDYYGTSYNFDYWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSSSSFS VSLGDRVTITCKANEDINNRLAWYQQTPGNSPRLLISGATNLVTGVPSRFSGSGSGK DYTLTITSLQAEDFATYYCQQYWSTPFTFGSGTELEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 51. In some alternatives, the scFv is encoded by the EGFR (cetuximab) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 52

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtgcagctgaaacagagcg gcccgggcctggtgcagccgagccagagcctgagcattacctgcaccgtgagcggctttagcctgaccaactatggcgtgcattgg gtgcgccagagcccgggcaaaggcctggaatggctgggcgtgatttggagcggcggcaacaccgattataacaccccgtttacca gccgcctgagcattaacaaagataacagcaaaagccaggtgtttttttaaaatgaacagcctgcagagcaacgataccgcgatttattat tgcgcgcgcgcgctgacctattatgattatgaatttgcgtattggggccagggcaccctggtgaccgtgagcgcgggcggcggcgg cagcggcggcggcggcagcggcggcggcggcagcgatattctgctgacccagagcccggtgattctgagcgtgagcccgggcg aacgcgtgagctttagctgccgcgcgagccagagcattggcaccaacattcattggtatcagcagcgcaccaacggcagcccgcgc ctgctgattaaatatgcgagcgaaagcattagcggcattccgagccgctttagcggcagcggcagcggcaccgattttaccctgagc attaacagcgtggaaagcgaagatattgcggattattattgccagcagaacaacaactggccgaccacctttggcgcgggcaccaaa ctggaactgaaacgcacc). In some alternatives, the scFv comprises the EGFR scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 53 (MLLLVTSLLLCELPHPAFLLIPQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHW VRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIY YCARALTYYDYEFAYWGQGTLVTVSAGGGGSGGGGSGGGGSDILLTQSPVILSVSP GERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSI NSVESEDIADYYCQQNNNWPTTFGAGTKLELKRT). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 53. In some alternatives, the scFv comprises the EGFRVIII (806) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by the EphA2 (2A4) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 56. In some alternatives, the scFv is encoded by the EpHA2 (4H5) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 58. In some alternatives, the scFv is encoded by a FITC (E2) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 60. In some alternatives, the scFv is encoded by an IL13Ra2 (hu08) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 68. In some alternatives, the scFv comprises an IL13Ra2 hu08 VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 69

(MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFSRNGMS
WVRQAPGKGLEWVATVSSGGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDT
AVYYCARQGTTALATRFFDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSS
LSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIYSASYRSTGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQHHYSAPWTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 69. In some alternatives, the scFv is encoded by an IL13Ra2 (hu07) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 70 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatattcagatgacccagagccc
gagcagcctgagcgcgagcgtgggcgatcgcgtgaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggt
atcagcagaaaccgggcaaagcgccgaaactgctgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcgg
cagcggcagcggcaccgattttaccctgaccattagcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgca
gcccgctgacctttggcggcggcaccaaagtggaaattaaaggtggtggtggttctggcggcggcggctccggtggtggtggttctg
aagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacct
ttaccaaatatggcgtgcattgggtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagca
ccgattataacagcgcgctgatgagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgc
gcgcggaagataccgcggtgtattattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtg
agcagcgaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 71 (MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCTASLSVSSTYLHWY
QQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCHQYHRSP
LTFGGGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFT
KYGVHWVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNS
LRAEDTAVYYCARDHRDAMDYWGQGTLVTVSSESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 71. In some alternatives, the scFv is encoded by the IL13Ra2 (hu07) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 72 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagaagtgcagctggtggaaagcg

gcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacctttaccaaatatggcgtgcattgg gtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagcaccgattataacagcgcgctgat gagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgcgcgcggaagataccgcggtgt attattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtgagcagcggtggtggtggttctg gcggcggcggctccggtggtggtggttctgatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatcgcgt gaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggtatcagcagaaaccgggcaaagcgccgaaactgc tgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcggcagcggcagcggcaccgattttaccctgaccatta gcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgcagcccgctgacctttggcggcggcaccaaagtgga aattaaagaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 73 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFTKYGVH WVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNSLRAED TAVYYCARDHRDAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCTASLSVSSTYLHWYQQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCHQYHRSPLTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 73. In some alternatives, the antibody or portion thereof or scFv is encoded by the Anti-IL13Ra2 (IL13 zetakine) nucleotide sequence. In some alternatives, the antibody or portion thereof or scFv is encoded by a sequence set forth in SEQ ID NO: 74 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaggccctgtgcctccctctacagcc ctcaggtacctcattgaggagctggtcaacatcacccagaaccagaaggctccgctctgcaatggcagcatggtatggagcatcaac ctgacagctggcatgtactgtgcagccctggaatccctgatcaacgtgtcaggctgcagtgccatcgagaagacccagaggatgctg agcggattctgcccgcacaaggtctcagctgggcagttttccagcttgcatgtccgagacaccaaaatcgaggtggcccagtttgtaa aggacctgctcttacatttaaagaaacttttcgcgagggacggttcaa). In some alternatives, the antibody or portion thereof or scFv comprises an Anti-IL13Ra2 (IL13 zetakine) amino acid sequence. In some alternatives, the antibody or portion thereof or scFv comprises an amino acid sequence set forth in SEQ ID NO: 75 (MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSI NLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQ

FVKDLLLHLKKLFREGRF). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 75. In some alternatives, the scFv is encoded by an oaGD2 (8B6) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 76

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatgttgtgatgacccaaactcca
ctctccctgcctgtcagtcttggagatcaagcctcaatctcttgcagatctagtcagagccttctaaaaaataatggaaacacctttttaca
ttggtacctgcagaagtcaggccagtctccaaagctccttatctacaaagtttccaaccgactttctggggtcccagacaggttcagtgg
cagtggatcagggacatatttcacactcaagatcagcagagtggaggctgaggatctgggagtttatttctgctctcaaagtacacatat
tccgtacacattcggaggggggaccaagctcgagctgaaacgaggcggaggggctctggcggcggaggatctgggggagggg
gcagcgaggtgaaactggtggagtctggaggaggcttggtgctgcctggggattctctgagactctcctgtgcaacttctgagttcac
cttcactgattactacatgacttgggtccgccagcctccaagaaaggcacttgagtggttgggttttattagaaacagagctaatggttac
acaacagagtacaatccatctgtgaagggtcggttcaccatttccagagataattcccaaagcatcctctatcttcaaatgaacaccctg
agaactgaggacagtgccacttattactgtgcaagagtctctaactgggcctttgactactggggccaaggcaccactctcacagtctc
ctca). In some alternatives, the scFv comprises the oaGD2 (8B6) VlVh scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 77

(MLLLVTSLLLCELPHPAFLLIPDVVMTQTPLSLPVSLGDQASISCRSSQSLLKNNGNT
FLHWYLQKSGQSPKLLIYKVSNRLSGVPDRFSGSGSGTYFTLKISRVEAEDLGVYFCS
QSTHIPYTFGGGTKLELKRGGGGSGGGGSGGGGSEVKLVESGGGLVLPGDSLRLSCA
TSEFTFTDYYMTWVRQPPRKALEWLGFIRNRANGYTTEYNPSVKGRFTISRDNSQSIL
YLQMNTLRTEDSATYYCARVSNWAFDYWGQGTTLTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 77. In some alternatives, the scFv is encoded by an ROR1 (R12) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 78

(atgctgctgctggtgacaagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggaacagctcgtcgaaagc
ggcggcagactggtgacacctggcggcagcctgaccctgagctgcaaggccagcggcttcgacttcagcgcctactacatgagctg
ggtccgccaggcccctggcaagggactggaatggatcgccaccatctaccccagcagcggcaagacctactacgccacctgggtg
aacggacggttcaccatctccagcgacaacgcccagaacaccgtggacctgcagatgaacagcctgacagccgccgaccgggcc
acctacttttgcgccagagacagctacgccgacgacggcgccctgttcaacatctggggccctggcaccctggtgacaatctctagc

ggcggaggcggatctggtggcggaggaagtggcggcggaggatctgagctggtgctgacccagagcccctctgtgtctgctgccc tgggaagccctgccaagatcacctgtaccctgagcagcgcccacaagaccgacaccatcgactggtatcagcagctgcagggcga ggcccccagatacctgatgcaggtgcagagcgacggcagctacaccaagaggccaggcgtgcccgaccggttcagcggatctag ctctggcgccgaccgctacctgatcatccccagcgtgcaggccgatgacgaggccgattactactgtggcgccgactacatcggcg gctacgtgttcggcggaggcacccagctgaccgtgaccggc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 79 (ROR1 (R12) scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQEQLVESGGRLVTPGGSLTLSCKASGFDFSAYYMSW VRQAPGKGLEWIATIYPSSGKTYYATWVNGRFTISSDNAQNTVDLQMNSLTAADRA TYFCARDSYADDGALFNIWGPGTLVTISSGGGGSGGGGSGGGGSELVLTQSPSVSAA LGSPAKITCTLSSAHKTDTIDWYQQLQGEAPRYLMQVQSDGSYTKRPGVPDRFSGSS SGADRYLIIPSVQADDEADYYCGADYIGGYVFGGGTQLTVTG). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 79. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 80 (CD33 (h2H12) VhVl scFv nucleotide sequence

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggttcagctggtgcagtctgga gctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggttacacctttaccaattatgatataaattgggtgag acaggcccctggacaagggcttgagtggattggatggatttatcctggagatggtagtaccaaatataatgagaaattcaaggccaag gctaccctgacagctgacacatccaccagcacagcctacatggagctgaggagcctgagatctgatgacacagctgtgtattactgtg cttctggatatgaagatgctatggactactgggggcaagggaccacagtcacagtctcctca). In some alternatives, the scFv is specific for CD33. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 81 (CD33 (h2H12) VhVl scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYDIN WVRQAPGQGLEWIGWIYPGDGSTKYNEKFKAKATLTADTSTSTAYMELRSLRSDDT AVYYCASGYEDAMDYWGQGTTVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 81. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 82 (CD33 (h2H12) VlVh scFv nucleotide sequence: atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagacatccagatgacccagtctccat cctcactgtctgcatctgtaggagacagagtcaccatcaattgtaaggctagtcaggacattaatagctatttgagctggtttcagcaga aaccagggaaagcccctaagaccctgatctatagagcaaatagattggtagatggggtcccatcaaggttctctggcagtggatctgg

gcaagattatactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgcttgcagtatgatgagtttcctctcacatttgg aggagggaccaaggtggagatcaaa). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 83 (CD33 (h2H12) VlVh scFv amino acid sequence: MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTINCKASQDINSYLSWFQ QKPGKAPKTLIYRANRLVDGVPSRFSGSGSGQDYTLTISSLQPEDFATYYCLQYDEFP LTFGGGTKVEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 83. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 84. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 86. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 87. In some alternatives, the spacer is encoded by the nucleic acid sequence set forth in SEQ ID NO: 102 (IgG4 hinge nucleotide sequence: gagagcaagtacggaccgccctgccccccttgccct). In some alternatives, the spacer comprises an amino acid sequence set forth in SEQ ID NO: 103 (IgG4 hinge amino acid sequence: ESKYGPPCPPCP). In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 103. In some alternatives, the spacer is encoded by a nucleic acid sequence set forth in SEQ ID NO: 104. In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives, HEA3 comprises two amino acid mutations, wherein the sequence is encoded by a sequence set forth in SEQ ID NO: 122 (atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacggcgaggacttcacccccccc atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac

caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc
agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag
ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct
gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc
ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagc
gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc
ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc
atggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga
tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct
gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga
tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc
ctgagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct
gctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca
cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt
ggagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcat
catgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagc
gtgcccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttcccca
gcggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccat
ggtgtctgcactggcccaggctccagctcctgtgcctgtgctgggcccctggacctcctcaggctgtggcccctcctgccccctaaacct
acccaggccgggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaata
gcaccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcc
ccacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccag
caccagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttca
gcgccctgctgtcccagatcagcagc). In some alternatives, the HEA3 comprises an amino acid sequence set forth in SEQ ID NO: 121 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF

SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM
DFSALLSQISS). This sequence comprises the sequence of HEA3 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA3(p65/S536E/K310Q). K310Q in RelA corresponds to position 621 in HEA3; S536E corresponds to position 846 in HEA3. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells is provided. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis. In some alternatives, genes that inhibit apoptosis include, for example, Bcl2, and/or CA-Akt. In some alternatives, the polypeptide is Bcl2 or CA-Akt. In some alternatives, genes that inhibit apoptosis include, for example, Survivin, Bcl2, CA-Akt, and/or dnCaspase3. In some alternatives, the polypeptide is Survivin, Bcl2, or CA-Akt and/or dnCaspase 3. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag
ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt
cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt
ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac
caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC
FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK
ETNNKKKEFEETVKKVRRAIEQLAAMD).

[0305] In some alternatives, a method of treating, inhibiting, or ameliorating a disease in a subject in need thereof is provided. The method comprises administering to the

subject the host cell, such as a mammalian cell, of any one of the alternatives herein, or at least one composition or product combination of any one or more of the alternatives herein. In some alternatives, the host cell, such as a mammalian cell, comprising a system of any one of the alternatives herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral specific molecule, and any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a

RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the

system, the second promoter is an inducible promoter. In some alternatives of the system, the second promoter is a constitutive promoter. In some alternatives of the system, the second promoter is the EF1αp. In some alternatives of the system, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system, the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system, selectable marker is EGFRt and/or HER2t. In some alternatives of the system, the selectable marker confers drug resistance. In some alternatives of the system, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which

encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of

the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the second nucleic acid further comprises: a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the system, the first promoter is in opposite orientation to the second promoter. In some alternatives of the system, the ligand binding domain is an antibody fragment, such as a binding fragment. In some alternatives of the system, the ligand binding domain is a single

chain variable fragment. In some alternatives of the system, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof. In some alternatives of the system, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the system, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives of the system, the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the host cell is a precursor T cell. In some alternatives, the precursor T cell is a hematopoietic stem cell. In some alternatives, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the composition comprises the host cell, such as a mammalian cell, of any one or more of the alternatives herein is provided, in a pharmaceutically acceptable excipient. In

some alternatives, the host cell, such as a mammalian cell, comprises a system of any one of the alternatives herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral molecule, and other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor

ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system, the second promoter is an inducible promoter. In some alternatives of the system, the second promoter is a constitutive promoter. In some alternatives of the system, the second promoter

is the EF1αp. In some alternatives of the system, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system, the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system, selectable marker is EGFRt and/or HER2t. In some alternatives of the system, the selectable marker confers drug resistance. In some alternatives of the system, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a

polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives

of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the second nucleic acid further comprises: a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the system, the first promoter is in opposite orientation to the second promoter. In some alternatives of the system, the ligand binding domain is an antibody fragment. In some alternatives of the system, the ligand binding domain is a single chain variable fragment. In some alternatives of the system, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3,

mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof. In some alternatives of the system, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the system, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives of the system, the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the host cell is a precursor T cell. In some alternatives, the precursor T cell is a hematopoietic stem cell. In some alternatives, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the composition comprises a host cell, wherein the host cell is a precursor T cell and a host cell wherein the host cell is a hematopoietic stem cell. In some alternatives, the composition comprises a host cell, wherein the host cell is a precursor T cell or a hematopoietic stem cell and a host cell that is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve

CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells or a CD4+ T cell selected from naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the disease is cancer or a viral disease. In some alternatives, the subject is identified or selected to receive an anti-cancer therapy. In some alternatives, the subject is identified or selected to receive an anti-viral therapy. In some alternatives, the method further comprises measuring or evaluating an inhibition of the disease. In some alternatives, the method further comprises providing said subject an additional anti-cancer therapy or anti-viral therapy before, during, or after administration of the cells of any one or more of the alternatives herein or at least one composition or product combination of any one or more of the alternatives herein. In some alternatives, the cells , such as mammalian cells, of any one or more of the aforementioned alternatives or at least one composition or product combination of any one or more of aforementioned alternatives are administered to said subject by adoptive cell transfer. In some alternatives, the host cells of any one or more of aforementioned alternatives or at least one composition or product combination of any one or more of the aforementioned alternatives are administered to said subject after said subject has received another form of anti-cancer therapy or anti-viral therapy. In some alternatives, the method further comprises administering a drug that induces expression of a transgene in the host cell or composition for the treatment of cancer or a viral infection. In some alternatives, the drug is tamoxifen and/or its metabolites, fulvestrant and/or other estrogen analogs or CMP8. In some alternatives, tamoxifen is administered at a dose range of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg/dose or within a range defined by any two of the aforementioned values. In some alternatives, the fulvestrant is administered at a dose range of 250, 300, 350, 400, 450 or 500 mg/dose mg/dose or within a range defined by any two of the aforementioned values. In some alternatives, the CMP8 is administered at a dose range to provide 30, 40 or 50 nM of drug levels in serum, or within a range defined by any two of the aforementioned values. In some alternatives, the cancer is a solid tumor or hematologic malignancy. In some alternatives, the solid tumor is selected from the group consisting of a breast cancer, brain cancer, lung cancer, colon cancer, renal cancer, pancreatic cancer, prostate cancer, and ovarian cancer. In some alternatives, the chimeric antigen receptor comprises a scFv. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv comprises an

huCD19 scFv (G01S) amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 41 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMH WVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDT AVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQ PRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSR SGRAASLIISGLQTEDEADYFCSSYAGRYNSVLFGGGTKLTVL). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 41. In some alternatives, the scFv is encoded by the muCD19 (FMC63) scFv nucleotide sequence. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 42 (Atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccgacatccagatgacccagac cacctccagcctgagcgccagcctgggcgaccgggtgaccatcagctgccgggccagccaggacatcagcaagtacctgaactg gtatcagcagaagcccgacggcaccgtcaagctgctgatctaccacaccagccggctgcacagcggcgtgcccagccggtttagc ggcagcggctccggcaccgactacagcctgaccatctccaacctggaacaggaagatatcgccacctacttttgccagcagggcaa cacactgccctacacctttggcggcggaacaaagctggaaatcaccggcagcacctccggcagcggcaagcctggcagcggcga gggcagcaccaagggcgaggtgaagctgcaggaaagcggccctggcctggtggcccccagccagagcctgagcgtgacctgca ccgtgagcggcgtgagcctgcccgactacggcgtgagctggatccggcagccccccaggaagggcctggaatggctgggcgtga tctggggcagcgagaccacctactacaacagcgccctgaagagccggctgaccatcatcaaggacaacagcaagagccaggtgtt cctgaagatgaacagcctgcagaccgacgacaccgccatctactactgcgccaagcactactactacggcggcagctacgccatgg actactggggccagggcaccagcgtgaccgtgagcagc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 43 (MLLLVTSLLLCELPHPAFLLIPDIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWY QQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLP YTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVSGVS LPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSL QTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 43. some alternatives, the scFv comprises a B7H3 (hBRCA84D) scFv nucleotide sequence. In some alternatives, the scFv binds specifically to

the B7-H3 receptor. In some alternatives, the scFv comprises the L1CAM (CE7) scFv nucleotide sequence. In some alternatives, the scFv is specific for the epitope, CE7 epitope, of L1CAM. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 50

(atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccaggtgcagctgcagcagcct
ggcgccgagctggtgaagccaggcgccagcgtgaagctgtcctgcaaggccagcggctacaccttcaccggctactggatgcact
gggtgaagcagagacccggccacggcctggaatggatcggcgagatcaaccccagcaacggccggaccaactacaacgagcgg
ttcaagagcaaggccaccctgaccgtggacaagagcagcaccaccgccttcatgcagctgtccggcctgaccagcgaggacagcg
ccgtgtacttctgcgccagggactactacggcaccagctacaacttcgactactggggccagggcaccacactgaccgtgagcagc
ggcggaggggctctggcggcggaggatctgggggaggggcagcgacatccagatgacccagagcagcagcagcttcagcg
tgagcctgggcgaccgggtgaccatcacctgtaaggccaacgaggacatcaacaaccggctggcctggtatcagcagacccccgg
caacagccccaggctgctgatcagcggcgccaccaacctggtgaccggcgtgcccagccggtttagcggcagcggctccggcaa
ggactacaccctgaccatcacaagcctgcaggccgaggacttcgccacctactactgccagcagtactggtccacccccttcaccttc
ggcagcggcaccgagctggaaatcaaa). In some alternatives, the scFv comprises the L1CAM (CE7) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 51

(MLLLVTSLLLCELPHPAFLLIPQVQLQQPGAELVKPGASVKLSCKASGYTFTGYWM
HWVKQRPGHGLEWIGEINPSNGRTNYNERFKSKATLTVDKSSTTAFMQLSGLTSEDS
AVYFCARDYYGTSYNFDYWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSSSSFS
VSLGDRVTITCKANEDINNRLAWYQQTPGNSPRLLISGATNLVTGVPSRFSGSGSGK
DYTLTITSLQAEDFATYYCQQYWSTPFTFGSGTELEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 51. In some alternatives, the scFv is encoded by the EGFR (cetuximab) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 52

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtgcagctgaaacagagcg
gcccgggcctggtgcagccgagccagagcctgagcattacctgcaccgtgagcggctttagcctgaccaactatggcgtgcattgg
gtgcgccagagcccgggcaaaggcctggaatggctgggcgtgatttggagcggcggcaacaccgattataacaccccgtttacca
gccgcctgagcattaacaaagataacagcaaaagccaggtgtttttaaaatgaacagcctgcagagcaacgataccgcgatttattat
tgcgcgcgcgcgctgacctattatgattatgaatttgcgtattggggccagggcaccctggtgaccgtgagcgcgggcggcggcgg

cagcggcggcggcggcagcggcggcggcggcagcgatattctgctgacccagagcccggtgattctgagcgtgagcccgggcg aacgcgtgagctttagctgccgcgcgagccagagcattggcaccaacattcattggtatcagcagcgcaccaacggcagcccgcgc ctgctgattaaatatgcgagcgaaagcattagcggcattccgagccgctttagcggcagcggcagcggcaccgattttaccctgagc attaacagcgtggaaagcgaagatattgcggattattattgccagcagaacaacaactggccgaccacctttggcgcgggcaccaaa ctggaactgaaacgcacc). In some alternatives, the scFv comprises the EGFR scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 53 (MLLLVTSLLLCELPHPAFLLIPQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHW VRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIY YCARALTYYDYEFAYWGQGTLVTVSAGGGGSGGGGSGGGGSDILLTQSPVILSVSP GERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSI NSVESEDIADYYCQQNNNWPTTFGAGTKLELKRT). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 53. In some alternatives, the scFv comprises the EGFRVIII (806) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by the EphA2 (2A4) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 56. In some alternatives, the scFv is encoded by the EpHA2 (4H5) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 58. In some alternatives, the scFv is encoded by a FITC (E2) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 60. In some alternatives, the scFv is encoded by an IL13Ra2 (hu08) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 68. In some alternatives, the scFv comprises an IL13Ra2 hu08 VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 69 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFSRNGMS WVRQAPGKGLEWVATVSSGGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARQGTTALATRFFDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSS LSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIYSASYRSTGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQHHYSAPWTFGGGTKVEIKESK). In some alternatives,

the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 69. In some alternatives, the scFv is encoded by an IL13Ra2 (hu07) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 70 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatattcagatgacccagagccc gagcagcctgagcgcgagcgtgggcgatcgcgtgaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggt atcagcagaaaccgggcaaagcgccgaaactgctgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcgg cagcggcagcggcaccgattttaccctgaccattagcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgca gcccgctgacctttggcggcggcaccaaagtggaaattaaaggtggtggtggttctggcggcggcggctccggtggtggtggttctg aagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacct ttaccaaatatggcgtgcattgggtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagca ccgattataacagcgcgctgatgagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgc gcgcggaagataccgcggtgtattattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtg agcagcgaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 71 (MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCTASLSVSSTYLHWY QQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCHQYHRSP LTFGGGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFT KYGVHWVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARDHRDAMDYWGQGTLVTVSSESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 71. In some alternatives, the scFv is encoded by the IL13Ra2 (hu07) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 72 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagaagtgcagctggtggaaagcg gcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacctttaccaaatatggcgtgcattgg gtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagcaccgattataacagcgcgctgat gagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgcgcgcggaagataccgcggtgt attattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtgagcagcggtggtggtggttctg gcggcggcggctccggtggtggtggttctgatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatcgcgt

gaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggtatcagcagaaaccgggcaaagcgccgaaactgc tgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcggcagcggcagcggcaccgattttaccctgaccatta gcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgcagcccgctgacctttggcggcggcaccaaagtgga aattaaagaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 73 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFTKYGVH WVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNSLRAED TAVYYCARDHRDAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCTASLSVSSTYLHWYQQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCHQYHRSPLTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 73. In some alternatives, the antibody or portion thereof or scFv is encoded by the Anti-IL13Ra2 (IL13 zetakine) nucleotide sequence. In some alternatives, the antibody or portion thereof or scFv is encoded by a sequence set forth in SEQ ID NO: 74 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaggccctgtgcctccctctacagcc ctcaggtacctcattgaggagctggtcaacatcacccagaaccagaaggctccgctctgcaatggcagcatggtatggagcatcaac ctgacagctggcatgtactgtgcagccctggaatccctgatcaacgtgtcaggctgcagtgccatcgagaagacccagaggatgctg agcggattctgcccgcacaaggtctcagctgggcagttttccagcttgcatgtccgagacaccaaaatcgaggtggcccagtttgtaa aggacctgctcttacatttaaagaaacttttcgcgagggacggttcaa). In some alternatives, the antibody or portion thereof or scFv comprises an Anti-IL13Ra2 (IL13 zetakine) amino acid sequence. In some alternatives, the antibody or portion thereof or scFv comprises an amino acid sequence set forth in SEQ ID NO: 75 (MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSI NLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQ FVKDLLLHLKKLFREGRF). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 75. In some alternatives, the scFv is encoded by an oaGD2 (8B6) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 76

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatgttgtgatgacccaaactcca ctctccctgcctgtcagtcttggagatcaagcctcaatctcttgcagatctagtcagagccttctaaaaaataatggaaacacctttttaca ttggtacctgcagaagtcaggccagtctccaaagctccttatctacaaagtttccaaccgactttctggggtcccagacaggttcagtgg cagtggatcagggacatatttcacactcaagatcagcagagtggaggctgaggatctgggagtttatttctgctctcaaagtacacatat tccgtacacattcggaggggggaccaagctcgagctgaaacgaggcggaggggctctggcggcggaggatctgggggagggg gcagcgaggtgaaactggtggagtctggaggaggcttggtgctgcctggggattctctgagactctcctgtgcaacttctgagttcac cttcactgattactacatgacttgggtccgccagcctccaagaaaggcacttgagtggttgggttttattagaaacagagctaatggttac acaacagagtacaatccatctgtgaagggtcggttcaccatttccagagataattcccaaagcatcctctatcttcaaatgaacaccctg agaactgaggacagtgccacttattactgtgcaagagtctctaactgggcctttgactactggggccaaggcaccactctcacagtctc ctca). In some alternatives, the scFv comprises the oaGD2 (8B6) VlVh scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 77 (MLLLVTSLLLCELPHPAFLLIPDVVMTQTPLSLPVSLGDQASISCRSSQSLLKNNGNT FLHWYLQKSGQSPKLLIYKVSNRLSGVPDRFSGSGSGTYFTLKISRVEAEDLGVYFCS QSTHIPYTFGGGTKLELKRGGGGSGGGGSGGGGSEVKLVESGGGLVLPGDSLRLSCA TSEFTFTDYYMTWVRQPPRKALEWLGFIRNRANGYTTEYNPSVKGRFTISRDNSQSIL YLQMNTLRTEDSATYYCARVSNWAFDYWGQGTTLTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 77. In some alternatives, the scFv is encoded by an ROR1 (R12) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 78 (atgctgctgctggtgacaagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggaacagctcgtcgaaagc ggcggcagactggtgacacctggcggcagcctgaccctgagctgcaaggccagcggcttcgacttcagcgcctactacatgagctg ggtccgccaggcccctggcaagggactggaatggatcgccaccatctaccccagcagcggcaagacctactacgccacctgggtg aacggacggttcaccatctccagcgacaacgcccagaacaccgtggacctgcagatgaacagcctgacagccgccgaccgggcc acctacttttgcgccagagacagctacgccgacgacggcgccctgttcaacatctggggccctggcaccctggtgacaatctctagc ggcggaggcggatctggtggcggaggaagtggcggcggaggatctgagctggtgctgacccagagcccctctgtgtctgctgccc tgggaagccctgccaagatcacctgtaccctgagcagcgcccacaagaccgacaccatcgactggtatcagcagctgcagggcga ggcccccagatacctgatgcaggtgcagagcgacggcagctacaccaagaggccaggcgtgcccgaccggttcagcggatctag ctctggcgccgaccgctacctgatcatccccagcgtgcaggccgatgacgaggccgattactactgtggcgccgactacatcggcg gctacgtgttcggcggaggcacccagctgaccgtgaccggc). In some alternatives, the scFv comprises an

amino acid sequence set forth in SEQ ID NO: 79 (ROR1 (R12) scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQEQLVESGGRLVTPGGSLTLSCKASGFDFSAYYMSW VRQAPGKGLEWIATIYPSSGKTYYATWVNGRFTISSDNAQNTVDLQMNSLTAADRA TYFCARDSYADDGALFNIWGPGTLVTISSGGGGSGGGGSGGGGSELVLTQSPSVSAA LGSPAKITCTLSSAHKTDTIDWYQQLQGEAPRYLMQVQSDGSYTKRPGVPDRFSGSS SGADRYLIIPSVQADDEADYYCGADYIGGYVFGGGTQLTVTG). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 79. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 80 (CD33 (h2H12) VhVl scFv nucleotide sequence (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggttcagctggtgcagtctgga gctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggttacacctttaccaattatgatataaattgggtgag acaggcccctggacaagggcttgagtggattggatggatttatcctggagatggtagtaccaaatataatgagaaattcaaggccaag gctaccctgacagctgacacatccaccagcacagcctacatggagctgaggagcctgagatctgatgacacagctgtgtattactgtg cttctggatatgaagatgctatggactactgggggcaagggaccacagtcacagtctcctca). In some alternatives, the scFv is specific for CD33. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 81 (CD33 (h2H12) VhVl scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYDIN WVRQAPGQGLEWIGWIYPGDGSTKYNEKFKAKATLTADTSTSTAYMELRSLRSDDT AVYYCASGYEDAMDYWGQGTTVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 81. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 82 (CD33 (h2H12) VlVh scFv nucleotide sequence: atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagacatccagatgacccagtctccat cctcactgtctgcatctgtaggagacagagtcaccatcaattgtaaggctagtcaggacattaatagctatttgagctggtttcagcaga aaccagggaaagcccctaagaccctgatctatagagcaaatagattggtagatggggtcccatcaaggttctctggcagtggatctgg gcaagattatactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgcttgcagtatgatgagtttcctctcacatttgg aggagggaccaaggtggagatcaaa). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 83 (CD33 (h2H12) VlVh scFv amino acid sequence: MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTINCKASQDINSYLSWFQ QKPGKAPKTLIYRANRLVDGVPSRFSGSGSGQDYTLTISSLQPEDFATYYCLQYDEFP

LTFGGGTKVEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 83. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 84. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 86. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 87. In some alternatives, the spacer is encoded by the nucleic acid sequence set forth in SEQ ID NO: 102 (IgG4 hinge nucleotide sequence: gagagcaagtacggaccgccctgccccccttgccct). In some alternatives, the spacer comprises an amino acid sequence set forth in SEQ ID NO: 103 (IgG4 hinge amino acid sequence: ESKYGPPCPPCP). In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 103. In some alternatives, the spacer is encoded by a nucleic acid sequence set forth in SEQ ID NO: 104. In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives, HEA3 comprises two amino acid mutations, wherein the sequence is encoded by a sequence set forth in SEQ ID NO: 122 (atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagc

gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc
ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc
atggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga
tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct
gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga
tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc
ctgagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct
gctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca
cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt
ggagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcat
catgaagaagtccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagc
gtgcccaagcctgccccccagccctacccttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttcccca
gcggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagccctgccat
ggtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacct
acccaggccggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaata
gcaccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcc
ccacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccag
caccagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttca
gcgccctgctgtcccagatcagcagc). In some alternatives, the HEA3 comprises an amino acid sequence set forth in SEQ ID NO: 121 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL
AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR
VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET

FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM DFSALLSQISS). This sequence comprises the sequence of HEA3 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA3(p65/S536E/K310Q). K310Q in RelA corresponds to position 621 in HEA3; S536E corresponds to position 846 in HEA3. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells is provided. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis. In some alternatives, genes that inhibit apoptosis include, for example, Bcl2, and/or CA-Akt. In some alternatives, the polypeptide is Bcl2 or CA-Akt. In some alternatives, genes that inhibit apoptosis include, for example, Survivin, Bcl2, CA-Akt, and/or dnCaspase3. In some alternatives, the polypeptide is Survivin, Bcl2, or CA-Akt and/or dnCaspase 3. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK ETNNKKKEFEETVKKVRRAIEQLAAMD).

[0306] In some alternatives, a use of the host cell, such as a mammalian cell, of any one of or more of the alternatives or at least one composition or product combination of any one or more of the alternatives in combination with a drug that induces expression of a transgene in the host cell, such as a mammalian cell, or composition for the treatment of cancer or a viral infection is provided. In some alternatives, the host cell, such as a mammalian cell comprises a system of any one of the alternatives herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells,

such as mammalian cells. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral molecule, and other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a

drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system, the second promoter is an inducible promoter. In some alternatives of the system, the second promoter is a constitutive promoter. In some alternatives of the system, the second promoter is the EF1αp. In some alternatives of the system, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system, the transcriptional activator is encoded by at least one nucleic acid

sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system, selectable marker is EGFRt and/or HER2t. In some alternatives of the system, the selectable marker confers drug resistance. In some alternatives of the system, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and b) a second nucleic acid comprising a second promoter, wherein the second

nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ

ID NO: 15, 16, 17 or 18. In some alternatives of the system, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the second nucleic acid further comprises: a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optionally optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the system, the first promoter is in opposite orientation to the second promoter. In some alternatives of the system, the ligand binding domain is an antibody fragment. In some alternatives of the system, the ligand binding domain is a single chain variable fragment. In some alternatives of the system, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof. In some alternatives of the system, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120

protein, or Epstein-Barr virus early antigen protein. In some alternatives of the system, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC or VAR2CSA. In some alternatives of the system, the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the host cell is a precursor T cell. In some alternatives, the precursor T cell is a hematopoietic stem cell. In some alternatives, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the composition comprises a host cell, such as a mammalian cell, of any one or more of the alternatives herein is provided, in a pharmaceutically acceptable excipient. In some alternatives, the host cell, preferably a mammalian cell, comprises a system of any one of the alternatives herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding

domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral molecule, and other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some

alternatives of the system, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system, the second promoter is an inducible promoter. In some alternatives of the system, the second promoter is a constitutive promoter. In some alternatives of the system, the second promoter is the EF1αp. In some alternatives of the system, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system, the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector.

In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system, selectable marker is EGFRt and/or HER2t. In some alternatives of the system, the selectable marker confers drug resistance. In some alternatives of the system, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3

chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the system,

the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the second nucleic acid further comprises: a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the system, the first promoter is in opposite orientation to the second promoter. In some alternatives of the system, the ligand binding domain is an antibody fragment, such as a binding fragment. In some alternatives of the system, the ligand binding domain is a single chain variable fragment. In some alternatives of the system, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof. In some alternatives of the system, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the system, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33,

Mesothelin, ROR-1, FITC or VAR2CSA. In some alternatives of the system, the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the host cell is a precursor T cell. In some alternatives, the precursor T cell is a hematopoietic stem cell. In some alternatives, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the composition comprises a host cell, wherein the host cell is a precursor T cell and a host cell wherein the host cell is a hematopoietic stem cell. In some alternatives, the composition comprises a host cell, wherein the host cell is a precursor T cell or a hematopoietic stem cell and a host cell that is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells or a CD4+ T cell selected from naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the drug is tamoxifen and/or its metabolites, fulvestrant and/or other estrogen analogs or CMP8. In some alternatives, tamoxifen is administered at a dose range of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg/dose or within a range defined by any two of

the aforementioned values. In some alternatives, the fulvestrant is administered at a dose range of 250, 300, 350, 400, 450 or 500 mg/dose or within a range defined by any two of the aforementioned values. In some alternatives, the CMP8 is administered at a dose range to provide 30, 40 or 50 nM of drug levels in serum, or within a range defined by any two of the aforementioned values. In some alternatives, the cancer is a solid tumor or hematologic malignancy. In some alternatives, the solid tumor is selected from the group consisting of a breast cancer, brain cancer, lung cancer, colon cancer, renal cancer, pancreatic cancer, prostate cancer, and ovarian cancer. In some alternatives, the chimeric antigen receptor comprises a scFv. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv comprises an huCD19 scFv (G01S) amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 41 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMH WVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDT AVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQ PRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSR SGRAASLIISGLQTEDEADYFCSSYAGRYNSVLFGGGTKLTVL). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 41. In some alternatives, the scFv is encoded by the muCD19 (FMC63) scFv nucleotide sequence. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 42 (Atgctgctgctggtgaccagcctgctgctgtgcgagctgccccacccgcctttctgctgatccccgacatccagatgacccagac cacctccagcctgagcgccagcctgggcgaccgggtgaccatcagctgccgggccagccaggacatcagcaagtacctgaactg gtatcagcagaagcccgacggcaccgtcaagctgctgatctaccacaccagccggctgcacagcggcgtgcccagccggtttagc ggcagcggctccggcaccgactacagcctgaccatctccaacctggaacaggaagatatcgccacctacttttgccagcagggcaa cacactgccctacacctttggcggcggaacaaagctggaaatcaccggcagcacctccggcagcggcaagcctggcagcggcga gggcagcaccaagggcgaggtgaagctgcaggaaagcggccctggcctggtggcccccagccagagcctgagcgtgacctgca ccgtgagcggcgtgagcctgcccgactacggcgtgagctggatccggcagccccccaggaagggcctggaatggctgggcgtga tctggggcagcgagaccacctactacaacagcgccctgaagagccggctgaccatcatcaaggacaacagcaagagccaggtgtt cctgaagatgaacagcctgcagaccgacgacaccgccatctactactgcgccaagcactactactacggcggcagctacgccatgg actactggggccagggcaccagcgtgaccgtgagcagc). In some alternatives, the scFv comprises an

amino acid sequence set forth in SEQ ID NO: 43 (MLLLVTSLLLCELPHPAFLLIPDIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWY QQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLP YTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVSGVS LPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSL QTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 43. some alternatives, the scFv comprises a B7H3 (hBRCA84D) scFv nucleotide sequence. In some alternatives, the scFv binds specifically to the B7-H3 receptor. In some alternatives, the scFv comprises the L1CAM (CE7) scFv nucleotide sequence. In some alternatives, the scFv is specific for the epitope, CE7 epitope, of L1CAM. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 50

(atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccaggtgcagctgcagcagcct ggcgccgagctggtgaagccaggcgccagcgtgaagctgtcctgcaaggccagcggctacaccttcaccggctactggatgcact gggtgaagcagagacccggccacggcctggaatggatcggcgagatcaaccccagcaacggccggaccaactacaacgagcgg ttcaagagcaaggccaccctgaccgtggacaagagcagcaccaccgccttcatgcagctgtccggcctgaccagcgaggacagcg ccgtgtacttctgcgccagggactactacggcaccagctacaacttcgactactggggccagggcaccacactgaccgtgagcagc ggcggaggggctctggcggcggaggatctgggggaggggcagcgacatccagatgacccagagcagcagcagcttcagcg tgagcctgggcgaccgggtgaccatcacctgtaaggccaacgaggacatcaacaaccggctggcctggtatcagcagacccccgg caacagccccaggctgctgatcagcggcgccaccaacctggtgaccggcgtgcccagccggtttagcggcagcggctccggcaa ggactacaccctgaccatcacaagcctgcaggccgaggacttcgccacctactactgccagcagtactggtccacccccttcaccttc ggcagcggcaccgagctggaaatcaaa). In some alternatives, the scFv comprises the L1CAM (CE7) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 51 (MLLLVTSLLLCELPHPAFLLIPQVQLQQPGAELVKPGASVKLSCKASGYTFTGYWM HWVKQRPGHGLEWIGEINPSNGRTNYNERFKSKATLTVDKSSTTAFMQLSGLTSEDS AVYFCARDYYGTSYNFDYWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSSSSFS VSLGDRVTITCKANEDINNRLAWYQQTPGNSPRLLISGATNLVTGVPSRFSGSGSGK DYTLTITSLQAEDFATYYCQQYWSTPFTFGSGTELEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the

amino acid sequence of SEQ ID NO: 51. In some alternatives, the scFv is encoded by the EGFR (cetuximab) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 52 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtgcagctgaaacagagcg gcccgggcctggtgcagccgagccagagcctgagcattacctgcaccgtgagcggctttagcctgaccaactatggcgtgcattgg gtgcgccagagcccgggcaaaggcctggaatggctgggcgtgatttggagcggcggcaacaccgattataacaccccgtttacca gccgcctgagcattaacaaagataacagcaaaagccaggtgtttttttaaaatgaacagcctgcagagcaacgataccgcgatttattat tgcgcgcgcgcgctgacctattatgattatgaatttgcgtattggggccagggcaccctggtgaccgtgagcgcgggcggcggcgg cagcggcggcggcggcagcggcggcggcggcagcgatattctgctgacccagagcccggtgattctgagcgtgagcccgggcg aacgcgtgagctttagctgccgcgcgagccagagcattggcaccaacattcattggtatcagcagcgcaccaacggcagcccgcgc ctgctgattaaatatgcgagcgaaagcattagcggcattccgagccgctttagcggcagcggcagcggcaccgattttaccctgagc attaacagcgtggaaagcgaagatattgcggattattattgccagcagaacaacaactggccgaccacctttggcgcgggcaccaaa ctggaactgaaacgcacc). In some alternatives, the scFv comprises the EGFR scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 53 (MLLLVTSLLLCELPHPAFLLIPQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHW VRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIY YCARALTYYDYEFAYWGQGTLVTVSAGGGGSGGGGSGGGGSDILLTQSPVILSVSP GERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSI NSVESEDIADYYCQQNNNWPTTFGAGTKLELKRT). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 53. In some alternatives, the scFv comprises the EGFRVIII (806) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by the EphA2 (2A4) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 56. In some alternatives, the scFv is encoded by the EpHA2 (4H5) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 58. In some alternatives, the scFv is encoded by a FITC (E2) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 60. In some alternatives, the scFv is encoded by an IL13Ra2 (hu08) VhVl scFv nucleotide

sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 68. In some alternatives, the scFv comprises an IL13Ra2 hu08 VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 69 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFSRNGMS WVRQAPGKGLEWVATVSSGGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARQGTTALATRFFDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSS LSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIYSASYRSTGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQHHYSAPWTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 69. In some alternatives, the scFv is encoded by an IL13Ra2 (hu07) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 70 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatattcagatgacccagagccc gagcagcctgagcgcgagcgtgggcgatcgcgtgaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggt atcagcagaaaccgggcaaagcgccgaaactgctgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcgg cagcggcagcggcaccgattttaccctgaccattagcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgca gcccgctgaccttggcggcggcaccaaagtggaaattaaaggtggtggtggttctggcggcggcggctccggtggtggtggttctg aagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacct ttaccaaatatggcgtgcattgggtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagca ccgattataacagcgcgctgatgagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgc gcgcggaagataccgcggtgtattattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtg agcagcgaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 71 (MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCTASLSVSSTYLHWY QQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCHQYHRSP LTFGGGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFT KYGVHWVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARDHRDAMDYWGQGTLVTVSSESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the

amino acid sequence of SEQ ID NO: 71. In some alternatives, the scFv is encoded by the IL13Ra2 (hu07) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 72 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagaagtgcagctggtggaaagcg gcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacctttaccaaatatggcgtgcattgg gtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagcaccgattataacagcgcgctgat gagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgcgcgcggaagataccgcggtgt attattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtgagcagcggtggtggtggttctg gcggcggcggctccggtggtggtggttctgatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatcgcgt gaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggtatcagcagaaaccgggcaaagcgccgaaactgc tgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcggcagcggcagcggcaccgattttaccctgaccatta gcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgcagcccgctgacctttggcggcggcaccaaagtgga aattaaagaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 73 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFTKYGVH WVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNSLRAED TAVYYCARDHRDAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCTASLSVSSTYLHWYQQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCHQYHRSPLTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 73. In some alternatives, the antibody or portion thereof or scFv is encoded by the Anti-IL13Ra2 (IL13 zetakine) nucleotide sequence. In some alternatives, the antibody or portion thereof or scFv is encoded by a sequence set forth in SEQ ID NO: 74 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaggccctgtgcctccctctacagcc ctcaggtacctcattgaggagctggtcaacatcacccagaaccagaaggctccgctctgcaatggcagcatggtatggagcatcaac ctgacagctggcatgtactgtgcagccctggaatccctgatcaacgtgtcaggctgcagtgccatcgagaagacccagaggatgctg agcggattctgcccgcacaaggtctcagctgggcagttttccagcttgcatgtccgagacaccaaaatcgaggtggcccagtttgtaa aggacctgctcttacatttaaagaaacttttcgcgagggacggttcaa). In some alternatives, the antibody or portion thereof or scFv comprises an Anti-IL13Ra2 (IL13 zetakine) amino acid sequence. In

some alternatives, the antibody or portion thereof or scFv comprises an amino acid sequence set forth in SEQ ID NO: 75 (MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSI NLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQ FVKDLLLHLKKLFREGRF). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 75. In some alternatives, the scFv is encoded by an oaGD2 (8B6) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 76

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatgttgtgatgacccaaactcca ctctccctgcctgtcagtcttggagatcaagcctcaatctcttgcagatctagtcagagccttctaaaaaataatggaaacacctttttaca ttggtacctgcagaagtcaggccagtctccaaagctccttatctacaaagtttccaaccgactttctggggtcccagacaggttcagtgg cagtggatcagggacatatttcacactcaagatcagcagagtggaggctgaggatctgggagtttatttctgctctcaaagtacacatat tccgtacacattcggaggggggaccaagctcgagctgaaacgaggcggaggggctctggcggcggaggatctgggggagggg gcagcgaggtgaaactggtggagtctggaggaggcttggtgctgcctggggattctctgagactctcctgtgcaacttctgagttcac cttcactgattactacatgacttgggtccgccagcctccaagaaaggcacttgagtggttgggttttattagaaacagagctaatggttac acaacagagtacaatccatctgtgaagggtcggttcaccatttccagagataattcccaaagcatcctctatcttcaaatgaacaccctg agaactgaggacagtgccacttattactgtgcaagagtctctaactgggcctttgactactggggccaaggcaccactctcacagtctc ctca). In some alternatives, the scFv comprises the oaGD2 (8B6) VlVh scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 77 (MLLLVTSLLLCELPHPAFLLIPDVVMTQTPLSLPVSLGDQASISCRSSQSLLKNNGNT FLHWYLQKSGQSPKLLIYKVSNRLSGVPDRFSGSGSGTYFTLKISRVEAEDLGVYFCS QSTHIPYTFGGGTKLELKRGGGGSGGGGSGGGGSEVKLVESGGGLVLPGDSLRLSCA TSEFTFTDYYMTWVRQPPRKALEWLGFIRNRANGYTTEYNPSVKGRFTISRDNSQSIL YLQMNTLRTEDSATYYCARVSNWAFDYWGQGTTLTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 77. In some alternatives, the scFv is encoded by an ROR1 (R12) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 78 (atgctgctgctggtgacaagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggaacagctcgtcgaaagc

ggcggcagactggtgacacctggcggcagcctgaccctgagctgcaaggccagcggcttcgacttcagcgcctactacatgagctg ggtccgccaggcccctggcaagggactggaatggatcgccaccatctaccccagcagcggcaagacctactacgccacctgggtg aacggacggttcaccatctccagcgacaacgcccagaacaccgtggacctgcagatgaacagcctgacagccgccgaccgggcc acctacttttgcgccagagacagctacgccgacgacggcgccctgttcaacatctggggccctggcaccctggtgacaatctctagc ggcggaggcggatctggtggcggaggaagtggcggcggaggatctgagctggtgctgacccagagcccctctgtgtctgctgccc tgggaagccctgccaagatcacctgtaccctgagcagcgcccacaagaccgacaccatcgactggtatcagcagctgcagggcga ggcccccagatacctgatgcaggtgcagagcgacggcagctacaccaagaggccaggcgtgcccgaccggttcagcggatctag ctctggcgccgaccgctacctgatcatccccagcgtgcaggccgatgacgaggccgattactactgtggcgccgactacatcggcg gctacgtgttcggcggaggcacccagctgaccgtgaccggc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 79 (ROR1 (R12) scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQEQLVESGGRLVTPGGSLTLSCKASGFDFSAYYMSW VRQAPGKGLEWIATIYPSSGKTYYATWVNGRFTISSDNAQNTVDLQMNSLTAADRA TYFCARDSYADDGALFNIWGPGTLVTISSGGGGSGGGGSGGGGSELVLTQSPSVSAA LGSPAKITCTLSSAHKTDTIDWYQQLQGEAPRYLMQVQSDGSYTKRPGVPDRFSGSS SGADRYLIIPSVQADDEADYYCGADYIGGYVFGGGTQLTVTG). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 79. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 80 (CD33 (h2H12) VhVl scFv nucleotide sequence

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggttcagctggtgcagtctgga gctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggttacacctttaccaattatgatataaattgggtgag acaggcccctggacaagggcttgagtggattggatggatttatcctggagatggtagtaccaaatataatgagaaattcaaggccaag gctaccctgacagctgacacatccaccagcacagcctacatggagctgaggagcctgagatctgatgacacagctgtgtattactgtg cttctggatatgaagatgctatggactactgggggcaagggaccacagtcacagtctcctca). In some alternatives, the scFv is specific for CD33. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 81 (CD33 (h2H12) VhVl scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYDIN WVRQAPGQGLEWIGWIYPGDGSTKYNEKFKAKATLTADTSTSTAYMELRSLRSDDT AVYYCASGYEDAMDYWGQGTTVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 81. In some alternatives, the scFv is encoded by a sequence set forth in SEQ

ID NO: 82 (CD33 (h2H12) VlVh scFv nucleotide sequence: atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagacatccagatgacccagtctccat cctcactgtctgcatctgtaggagacagagtcaccatcaattgtaaggctagtcaggacattaatagctatttgagctggtttcagcaga aaccagggaaagcccctaagaccctgatctatagagcaaatagattggtagatggggtcccatcaaggttctctggcagtggatctgg gcaagattatactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgcttgcagtatgatgagtttcctctcacatttgg aggagggaccaaggtggagatcaaa). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 83 (CD33 (h2H12) VlVh scFv amino acid sequence: MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTINCKASQDINSYLSWFQ QKPGKAPKTLIYRANRLVDGVPSRFSGSGSGQDYTLTISSLQPEDFATYYCLQYDEFP LTFGGGTKVEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 83. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 84. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 86. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 87. In some alternatives, the spacer is encoded by the nucleic acid sequence set forth in SEQ ID NO: 102 (IgG4 hinge nucleotide sequence: gagagcaagtacggaccgccctgccccccttgccct). In some alternatives, the spacer comprises an amino acid sequence set forth in SEQ ID NO: 103 (IgG4 hinge amino acid sequence: ESKYGPPCPPCP). In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 103. In some alternatives, the spacer is encoded by a nucleic acid sequence set forth in SEQ ID NO: 104. In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives, HEA3 comprises two amino acid mutations, wherein the sequence is encoded by a sequence set forth in SEQ ID NO: 122 (atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc

atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc
tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac
cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg
aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac
caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc
agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag
ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct
gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc
ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccctatcctgtacagcgagtacgaccccaccagacccttcagc
gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc
ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc
atggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga
tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct
gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga
tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc
ctgagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct
gctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca
cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt
ggagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcat
catgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagc
gtgcccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttcccca
gcggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccat
ggtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacct
acccaggccggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaata
gcaccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcc
ccacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccag
caccagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttca
gcgccctgctgtcccagatcagcagc). In some alternatives, the HEA3 comprises an amino acid sequence set forth in SEQ ID NO: 121 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR

VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM
DFSALLSQISS). This sequence comprises the sequence of HEA3 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA3(p65/S536E/K310Q). K310Q in RelA corresponds to position 621 in HEA3; S536E corresponds to position 846 in HEA3. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells is provided. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis. In some alternatives, genes that inhibit apoptosis include, for example, Bcl2, and/or CA-Akt. In some alternatives, the polypeptide is Bcl2 or CA-Akt. In some alternatives, genes that inhibit apoptosis include, for example, Survivin, Bcl2, CA-Akt, and/or dnCaspase3. In some alternatives, the polypeptide is Survivin, Bcl2, or CA-Akt and/or dnCaspase 3. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag
ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt
cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt
ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac
caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC

FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK ETNNKKKEFEETVKKVRRAIEQLAAMD).

[0307] In some alternatives, a method of performing cellular immunotherapy in a subject having cancer or a viral infection is provided. The method comprises administering the host cells, such as mammalian cells, of any one or more of the alternatives herein or at least one composition or product combination of any one or more of the alternatives herein to the subject and administering a drug that induces expression of a transgene in the composition or the host cells, such as mammalian cells. In some alternatives, the host cell, such as a mammalian cell, comprises a system of any one of the alternatives herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral molecule, and other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one

mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing

expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system, the second promoter is an inducible promoter. In some alternatives of the system, the second promoter is a constitutive promoter. In some alternatives of the system, the second promoter is the EF1αp. In some alternatives of the system, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system, the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system, selectable marker is EGFRt and/or HER2t. In some alternatives of the system, the selectable marker confers drug resistance. In some alternatives of the system, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence

identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a

drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the second nucleic acid further comprises: a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the

spacer is optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the system, the first promoter is in opposite orientation to the second promoter. In some alternatives of the system, the ligand binding domain is an antibody fragment. In some alternatives of the system, the ligand binding domain is a single chain variable fragment. In some alternatives of the system, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof. In some alternatives of the system, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the system, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC or VAR2CSA. In some alternatives of the system, the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the host cell is a precursor T cell. In some alternatives, the precursor T cell is a hematopoietic stem cell. In some alternatives, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+

T cells. In some alternatives, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the composition comprises a host cell, such as a mammalian cell, of any one or more of the alternatives herein, in a pharmaceutically acceptable excipient. In some alternatives, the host cell, such as a mammalian cell, comprises a system of any one of the alternatives herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral specific molecule, and other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least

one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain,

nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system, the second promoter is an inducible promoter. In some alternatives of the system, the second promoter is a constitutive promoter. In some alternatives of the system, the second promoter is the EF1αp. In some alternatives of the system, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system, the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system, selectable marker is EGFRt and/or HER2t. In some alternatives of the system, the selectable marker confers drug resistance. In some alternatives of the system, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell

function. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some

alternatives of the system, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the second nucleic acid further comprises: a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the system, the first promoter is in opposite orientation to the second promoter. In some

alternatives of the system, the ligand binding domain is an antibody fragment, such as a binding fragment. In some alternatives of the system, the ligand binding domain is a single chain variable fragment. In some alternatives of the system, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof. In some alternatives of the system, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the system, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC or VAR2CSA. In some alternatives of the system, the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the host cell is a precursor T cell. In some alternatives, the precursor T cell is a hematopoietic stem cell. In some alternatives, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some

alternatives, the composition comprises a host cell, wherein the host cell is a precursor T cell and a host cell wherein the host cell is a hematopoietic stem cell. In some alternatives, the composition comprises a host cell, wherein the host cell is a precursor T cell or a hematopoietic stem cell and a host cell that is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells or a CD4+ T cell selected from naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the cancer is selected from a solid tumor or hematologic malignancy. In some alternatives, the solid tumor is selected from the group consisting of a breast cancer, brain cancer, lung cancer, colon cancer, renal cancer, pancreatic cancer, prostate cancer, and ovarian cancer. In some alternatives, the chimeric antigen receptor comprises a scFv. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv comprises an huCD19 scFv (G01S) amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 41 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMH WVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDT AVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQ PRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSR SGRAASLIISGLQTEDEADYFCSSYAGRYNSVLFGGGTKLTVL). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 41. In some alternatives, the scFv is encoded by the muCD19 (FMC63) scFv nucleotide sequence. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 42 (Atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatccccgacatccagatgacccagac cacctccagcctgagcgccagcctgggcgaccgggtgaccatcagctgccgggccagccaggacatcagcaagtacctgaactg gtatcagcagaagcccgacggcaccgtcaagctgctgatctaccacaccagccggctgcacagcggcgtgcccagccggtttagc ggcagcggctccggcaccgactacagcctgaccatctccaacctggaacaggaagatatcgccacctacttttgccagcagggcaa cacactgccctacacctttggcggcggaacaaagctggaaatcaccggcagcacctccggcagcggcaagcctggcagcggcga gggcagcaccaagggcgaggtgaagctgcaggaaagcggccctggcctggtggcccccagccagagcctgagcgtgacctgca ccgtgagcggcgtgagcctgcccgactacggcgtgagctggatccggcagcccccaggaagggcctggaatggctgggcgtga

tctggggcagcgagaccacctactacaacagcgccctgaagagccggctgaccatcatcaaggacaacagcaagagccaggtgtt cctgaagatgaacagcctgcagaccgacgacaccgccatctactactgcgccaagcactactactacggcggcagctacgccatgg actactggggccagggcaccagcgtgaccgtgagcagc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 43 (MLLLVTSLLLCELPHPAFLLIPDIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWY QQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLP YTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVSGVS LPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSL QTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 43. some alternatives, the scFv comprises a B7H3 (hBRCA84D) scFv nucleotide sequence. In some alternatives, the scFv binds specifically to the B7-H3 receptor. In some alternatives, the scFv comprises the L1CAM (CE7) scFv nucleotide sequence. In some alternatives, the scFv is specific for the epitope, CE7 epitope, of L1CAM. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 50

(atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggtgcagctgcagcagcct ggcgccgagctggtgaagccaggcgccagcgtgaagctgtcctgcaaggccagcggctacaccttcaccggctactggatgcact gggtgaagcagagacccggccacggcctggaatggatcggcgagatcaaccccagcaacggccggaccaactacaacgagcgg ttcaagagcaaggccaccctgaccgtggacaagagcagcaccaccgccttcatgcagctgtccggcctgaccagcgaggacagcg ccgtgtacttctgcgccagggactactacggcaccagctacaacttcgactactggggccagggcaccacactgaccgtgagcagc ggcggaggggctctggcggcggaggatctgggggaggggcagcgacatccagatgacccagagcagcagcagcttcagcg tgagcctgggcgaccgggtgaccatcacctgtaaggccaacgaggacatcaacaaccggctggcctggtatcagcagacccccgg caacagccccaggctgctgatcagcggcgccaccaacctggtgaccggcgtgcccagccggtttagcggcagcggctccggcaa ggactacaccctgaccatcacaagcctgcaggccgaggacttcgccacctactactgccagcagtactggtccacccccttcaccttc ggcagcggcaccgagctggaaatcaaa). In some alternatives, the scFv comprises the L1CAM (CE7) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 51 (MLLLVTSLLLCELPHPAFLLIPQVQLQQPGAELVKPGASVKLSCKASGYTFTGYWM HWVKQRPGHGLEWIGEINPSNGRTNYNERFKSKATLTVDKSSTTAFMQLSGLTSEDS AVYFCARDYYGTSYNFDYWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSSSSFS

VSLGDRVTITCKANEDINNRLAWYQQTPGNSPRLLISGATNLVTGVPSRFSGSGSGK DYTLTITSLQAEDFATYYCQQYWSTPFTFGSGTELEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 51. In some alternatives, the scFv is encoded by the EGFR (cetuximab) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 52 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtgcagctgaaacagagcg gcccgggcctggtgcagccgagccagagcctgagcattacctgcaccgtgagcggctttagcctgaccaactatggcgtgcattgg gtgcgccagagcccgggcaaaggcctggaatggctgggcgtgatttggagcggcggcaacaccgattataacaccccgtttacca gccgcctgagcattaacaaagataacagcaaaagccaggtgtttttttaaaatgaacagcctgcagagcaacgataccgcgatttattat tgcgcgcgcgcgctgacctattatgattatgaatttgcgtattggggccagggcaccctggtgaccgtgagcgcgggcggcggcgg cagcggcggcggcggcagcggcggcggcggcagcgatattctgctgacccagagcccggtgattctgagcgtgagccccgggcg aacgcgtgagctttagctgccgcgcgagccagagcattggcaccaacattcattggtatcagcagcgcaccaacggcagcccgcgc ctgctgattaaatatgcgagcgaaagcattagcggcattccgagccgctttagcggcagcggcagcggcaccgattttaccctgagc attaacagcgtggaaagcgaagatattgcggattattattgccagcagaacaacaactggccgaccacctttggcgcgggcaccaaa ctggaactgaaacgcacc). In some alternatives, the scFv comprises the EGFR scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 53 (MLLLVTSLLLCELPHPAFLLIPQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHW VRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIY YCARALTYYDYEFAYWGQGTLVTVSAGGGGSGGGGSGGGGSDILLTQSPVILSVSP GERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSI NSVESEDIADYYCQQNNNWPTTFGAGTKLELKRT). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 53. In some alternatives, the scFv comprises the EGFRVIII (806) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by the EphA2 (2A4) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 56. In some alternatives, the scFv is encoded by the EpHA2 (4H5) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO:

58. In some alternatives, the scFv is encoded by a FITC (E2) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 60. In some alternatives, the scFv is encoded by an IL13Ra2 (hu08) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 68. In some alternatives, the scFv comprises an IL13Ra2 hu08 VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 69 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFSRNGMS WVRQAPGKGLEWVATVSSGGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARQGTTALATRFFDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSS LSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIYSASYRSTGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQHHYSAPWTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 69. In some alternatives, the scFv is encoded by an IL13Ra2 (hu07) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 70 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatattcagatgacccagagccc gagcagcctgagcgcgagcgtgggcgatcgcgtgaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggt atcagcagaaaccgggcaaagcgccgaaactgctgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcgg cagcggcagcggcaccgattttaccctgaccattagcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgca gcccgctgaccttggcggcggcaccaaagtggaaattaaaggtggtggtggttctggcggcggcggctccggtggtggtggttctg aagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacct ttaccaaatatggcgtgcattgggtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagca ccgattataacagcgcgctgatgagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgc gcgcggaagataccgcggtgtattattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtg agcagcgaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 71 (MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCTASLSVSSTYLHWY QQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCHQYHRSP LTFGGGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFT

KYGVHWVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARDHRDAMDYWGQGTLVTVSSESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 71. In some alternatives, the scFv is encoded by the IL13Ra2 (hu07) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 72 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagaagtgcagctggtggaaagcg gcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacctttaccaaatatggcgtgcattgg gtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagcaccgattataacagcgcgctgat gagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgcgcgcggaagataccgcggtgt attattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtgagcagcggtggtggtggttctg gcggcggcggctccggtggtggtggttctgatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatcgcgt gaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggtatcagcagaaaccgggcaaagcgccgaaactgc tgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcggcagcggcagcggcaccgattttaccctgaccatta gcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgcagcccgctgacctttggcggcggcaccaaagtgga aattaaagaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 73 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFTKYGVH WVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNSLRAED TAVYYCARDHRDAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCTASLSVSSTYLHWYQQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCHQYHRSPLTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 73. In some alternatives, the antibody or portion thereof or scFv is encoded by the Anti-IL13Ra2 (IL13 zetakine) nucleotide sequence. In some alternatives, the antibody or portion thereof or scFv is encoded by a sequence set forth in SEQ ID NO: 74 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaggccctgtgcctccctctacagcc ctcaggtacctcattgaggagctggtcaacatcacccagaaccagaaggctccgctctgcaatggcagcatggtatggagcatcaac ctgacagctggcatgtactgtgcagccctggaatccctgatcaacgtgtcaggctgcagtgccatcgagaagacccagaggatgctg

agcggattctgcccgcacaaggtctcagctgggcagttttccagcttgcatgtccgagacaccaaaatcgaggtggcccagtttgtaa aggacctgctcttacatttaaagaaacttttcgcgagggacggttcaa). In some alternatives, the antibody or portion thereof or scFv comprises an Anti-IL13Ra2 (IL13 zetakine) amino acid sequence. In some alternatives, the antibody or portion thereof or scFv comprises an amino acid sequence set forth in SEQ ID NO: 75 (MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSI NLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQ FVKDLLLHLKKLFREGRF). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 75. In some alternatives, the scFv is encoded by an oaGD2 (8B6) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 76

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatgttgtgatgacccaaactcca ctctccctgcctgtcagtcttggagatcaagcctcaatctcttgcagatctagtcagagccttctaaaaaataatggaaacacctttttaca ttggtacctgcagaagtcaggccagtctccaaagctccttatctacaaagtttccaaccgactttctggggtcccagacaggttcagtgg cagtggatcagggacatatttcacactcaagatcagcagagtggaggctgaggatctgggagtttatttctgctctcaaagtacacatat tccgtacacattcggaggggggaccaagctcgagctgaaacgaggcggaggggctctggcggcggaggatctgggggagggg gcagcgaggtgaaactggtggagtctggaggaggcttggtgctgcctggggattctctgagactctcctgtgcaacttctgagttcac cttcactgattactacatgacttgggtccgccagcctccaagaaaggcacttgagtggttgggttttattagaaacagagctaatggttac acaacagagtacaatccatctgtgaagggtcggttcaccatttccagagataattcccaaagcatcctctatcttcaaatgaacaccctg agaactgaggacagtgccacttattactgtgcaagagtctctaactgggcctttgactactggggccaaggcaccactctcacagtctc ctca). In some alternatives, the scFv comprises the oaGD2 (8B6) VlVh scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 77 (MLLLVTSLLLCELPHPAFLLIPDVVMTQTPLSLPVSLGDQASISCRSSQSLLKNNGNT FLHWYLQKSGQSPKLLIYKVSNRLSGVPDRFSGSGSGTYFTLKISRVEAEDLGVYFCS QSTHIPYTFGGGTKLELKRGGGGSGGGGSGGGGSEVKLVESGGGLVLPGDSLRLSCA TSEFTFTDYYMTWVRQPPRKALEWLGFIRNRANGYTTEYNPSVKGRFTISRDNSQSIL YLQMNTLRTEDSATYYCARVSNWAFDYWGQGTTLTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 77. In some alternatives, the scFv is encoded by an

ROR1 (R12) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 78 (atgctgctgctggtgacaagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggaacagctcgtcgaaagc ggcggcagactggtgacacctggcggcagcctgaccctgagctgcaaggccagcggcttcgacttcagcgcctactacatgagctg ggtccgccaggcccctggcaagggactggaatggatcgccaccatctaccccagcagcggcaagacctactacgccacctgggtg aacggacggttcaccatctccagcgacaacgcccagaacaccgtggacctgcagatgaacagcctgacagccgccgaccgggcc acctacttttgcgccagagacagctacgccgacgacggcgccctgttcaacatctggggccctggcaccctggtgacaatctctagc ggcggaggcggatctggtggcggaggaagtggcggcggaggatctgagctggtgctgacccagagcccctctgtgtctgctgccc tgggaagccctgccaagatcacctgtaccctgagcagcgcccacaagaccgacaccatcgactggtatcagcagctgcagggcga ggcccccagatacctgatgcaggtgcagagcgacggcagctacaccaagaggccaggcgtgcccgaccggttcagcggatctag ctctggcgccgaccgctacctgatcatccccagcgtgcaggccgatgacgaggccgattactactgtggcgccgactacatcggcg gctacgtgttcggcggaggcacccagctgaccgtgaccggc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 79 (ROR1 (R12) scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQEQLVESGGRLVTPGGSLTLSCKASGFDFSAYYMSW VRQAPGKGLEWIATIYPSSGKTYYATWVNGRFTISSDNAQNTVDLQMNSLTAADRA TYFCARDSYADDGALFNIWGPGTLVTISSGGGGSGGGGSGGGGSELVLTQSPSVSAA LGSPAKITCTLSSAHKTDTIDWYQQLQGEAPRYLMQVQSDGSYTKRPGVPDRFSGSS SGADRYLIIPSVQADDEADYYCGADYIGGYVFGGGTQLTVTG). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 79. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 80 (CD33 (h2H12) VhVl scFv nucleotide sequence

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggttcagctggtgcagtctgga gctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggttacacctttaccaattatgatataaattgggtgag acaggcccctggacaagggcttgagtggattggatggatttatcctggagatggtagtaccaaatataatgagaaattcaaggccaag gctaccctgacagctgacacatccaccagcacagcctacatggagctgaggagcctgagatctgatgacacagctgtgtattactgtg cttctggatatgaagatgctatggactactgggggcaagggaccacagtcacagtctcctca). In some alternatives, the scFv is specific for CD33. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 81 (CD33 (h2H12) VhVl scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYDIN WVRQAPGQGLEWIGWIYPGDGSTKYNEKFKAKATLTADTSTSTAYMELRSLRSDDT

AVYYCASGYEDAMDYWGQGTTVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 81. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 82 (CD33 (h2H12) VlVh scFv nucleotide sequence: atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagacatccagatgacccagtctccat cctcactgtctgcatctgtaggagacagagtcaccatcaattgtaaggctagtcaggacattaatagctatttgagctggtttcagcaga aaccagggaaagcccctaagaccctgatctatagagcaaatagattggtagatggggtcccatcaaggttctctggcagtggatctgg gcaagattatactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgcttgcagtatgatgagtttcctctcacatttgg aggagggaccaaggtggagatcaaa). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 83 (CD33 (h2H12) VlVh scFv amino acid sequence: MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTINCKASQDINSYLSWFQ QKPGKAPKTLIYRANRLVDGVPSRFSGSGSGQDYTLTISSLQPEDFATYYCLQYDEFP LTFGGGTKVEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 83. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 84. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 86. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 87. In some alternatives, the spacer is encoded by the nucleic acid sequence set forth in SEQ ID NO: 102 (IgG4 hinge nucleotide sequence: gagagcaagtacggaccgccctgccccccttgccct). In some alternatives, the spacer comprises an amino acid sequence set forth in SEQ ID NO: 103 (IgG4 hinge amino acid sequence: ESKYGPPCPPCP). In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 103. In some alternatives, the spacer is encoded by a nucleic acid sequence set forth in SEQ ID NO: 104. In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives, HEA3 comprises two amino acid mutations, wherein the sequence is encoded by a sequence set forth in SEQ ID NO: 122

(atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg
cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct
ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc
atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc
tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac
cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg
aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac
caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc
agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag
ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct
gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc
ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccccctatcctgtacagcgagtacgaccccaccagacccttcagc
gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc
ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc
atggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga
tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct
gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga
tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc
ctgagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct
gctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca
cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt
ggagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcat
catgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagc
gtgcccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttcccca
gcggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccat
ggtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacct
acccaggccgggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaata
gcaccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcc
ccacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccag
caccagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttca
gcgccctgctgtcccagatcagcagc). In some alternatives, the HEA3 comprises an amino acid

sequence set forth in SEQ ID NO: 121 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM DFSALLSQISS). This sequence comprises the sequence of HEA3 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA3(p65/S536E/K310Q). K310Q in RelA corresponds to position 621 in HEA3; S536E corresponds to position 846 in HEA3. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells is provided. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis. In some alternatives, genes that inhibit apoptosis include, for example, Bcl2, and/or CA-Akt. In some alternatives, the polypeptide is Bcl2 or CA-Akt. In some alternatives, genes that inhibit apoptosis include, for example, Survivin, Bcl2, CA-Akt, and/or dnCaspase3. In some alternatives, the polypeptide is Survivin, Bcl2, or CA-Akt and/or dnCaspase 3. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac

caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK ETNNKKKEFEETVKKVRRAIEQLAAMD).

[0308] In some alternatives, a use of the host cell, such as a mammalian cell, of any one of or more of the alternatives herein or at least one composition or product combination of any one or more of alternatives herein as a medicament, is provided. In some alternatives, the host cell, such as a mammalian cell, comprises a system of any one of the alternatives herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells, such as mammalian cells. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral specific molecule, and any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and

wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases,

eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system, the second promoter is an inducible promoter. In some alternatives of the system, the second promoter is a constitutive promoter. In some alternatives of the system, the second promoter is the EF1αp. In some alternatives of the system, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system, the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system, selectable marker is EGFRt and/or HER2t. In some alternatives of the system, the selectable marker confers drug resistance. In some alternatives of the system, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has

95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives, the system is for inducible expression of a gene that regulates a T cell function. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation

domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the second nucleic acid further comprises: a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or

elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the system, the first promoter is in opposite orientation to the second promoter. In some alternatives of the system, the ligand binding domain is an antibody fragment. In some alternatives of the system, the ligand binding domain is a single chain variable fragment. In some alternatives of the system, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof. In some alternatives of the system, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the system, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC or VAR2CSA. In some alternatives of the system, the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the host cell is a precursor T cell. In some alternatives, the precursor T cell is a hematopoietic stem cell. In some alternatives, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve

CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the composition comprises a host cell of any one or more of the alternatives herein is provided, in a pharmaceutically acceptable excipient. In some alternatives, the host cell comprises a system of any one of the alternatives herein. In some alternatives, the system is for inducible expression of a chimeric antigen receptor in cells. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral specific molecule, and other molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte, a second polynucleotide, which encodes a spacer preferably an optimized polypeptide spacer, a third polynucleotide, which encodes a transmembrane domain and a fourth polynucleotide, which encodes an intracellular signaling domain and b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65)

transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23. In some alternatives of the system, the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema,

fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain. In some alternatives of the system, the second promoter is an inducible promoter. In some alternatives of the system, the second promoter is a constitutive promoter. In some alternatives of the system, the second promoter is the EF1αp. In some alternatives of the system, the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121. In some alternatives of the system, the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives of the system, the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker. In some alternatives of the system, the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker. In some alternatives of the system, selectable marker is EGFRt and/or HER2t. In some alternatives of the system, the selectable marker confers drug resistance. In some alternatives of the system, the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide. In some alternatives of the system, the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide. In some alternatives of the system, the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence of 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some

that has alternatives, the system is for inducible expression of a gene that regulates a T cell function. The system comprises a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3. In some alternatives of the system, the transcriptional activator is HEA3 or HEA4. In some alternatives of the system, HEA3 is a variant of a wild type HEA3 transcription factor. In some alternatives of the system, HEA4 is a variant of a wild type HEA4 transcription factor. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand. In some alternatives of the system, HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug. In some alternatives of the system, the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid

substitutions that enhance transcriptional activity in response to the drug ligand. In some alternatives of the system, the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121. In some alternatives of the system, the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122. In some alternatives of the system, the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7. In some alternatives of the system, the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18. In some alternatives of the system, the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug. In some alternatives of the system, the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8. In some alternatives of the system, the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values. In some alternatives of the system, the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero. In some alternatives of the system, the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor. In some alternatives of the system, the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss. In some alternatives of the system, the second nucleic acid further comprises: a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral molecule, or another molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; a polynucleotide coding for a transmembrane domain; and a polynucleotide encoding an intracellular signaling domain. In some alternatives of the

system, the first promoter is in opposite orientation to the second promoter. In some alternatives of the system, the ligand binding domain is an antibody fragment. In some alternatives of the system, the ligand binding domain is a single chain variable fragment. In some alternatives of the system, the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof. In some alternatives of the system, the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein. In some alternatives of the system, the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA. In some alternatives of the system, the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3. In some alternatives of the system, the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor. In some alternatives of the system, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120. In some alternatives of the system, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives of the system, the DNA spacer enhances gene expression of the chimeric antigen receptor. In some alternatives of the system, the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector. In some alternatives of the system, both vectors are packaged in a viral vector. In some alternatives of the system, the viral vector is an adeno-associated virus or a lentivirus. In some alternatives, the host cell is a precursor T cell. In some alternatives, the precursor T cell is a hematopoietic stem cell. In some alternatives, the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells. In some alternatives, the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector

memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the composition comprises a host cell, wherein the host cell is a precursor T cell and a host cell wherein the host cell is a hematopoietic stem cell. In some alternatives, the composition comprises a host cell, wherein the host cell is a precursor T cell or a hematopoietic stem cell and a host cell that is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells or a CD4+ T cell selected from naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some alternatives, the chimeric antigen receptor comprises a scFv. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv comprises an huCD19 scFv (G01S) amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 41 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMH WVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDT AVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQ PRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSR SGRAASLIISGLQTEDEADYFCSSYAGRYNSVLFGGGTKLTVL). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 41. In some alternatives, the scFv is encoded by the muCD19 (FMC63) scFv nucleotide sequence. In some alternatives, the scFv specifically binds to CD19. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 42 (Atgctgctgctggtgaccagcctgctgctgtgcgagctgccccacccgcctttctgctgatccccgacatccagatgacccagac cacctccagcctgagcgccagcctgggcgaccgggtgaccatcagctgccgggccagccaggacatcagcaagtacctgaactg gtatcagcagaagcccgacggcaccgtcaagctgctgatctaccacaccagccggctgcacagcggcgtgcccagccggtttagc ggcagcggctccggcaccgactacagcctgaccatctccaacctggaacaggaagatatcgccacctacttttgccagcagggcaa cacactgccctacacctttggcggcggaacaaagctggaaatcaccggcagcacctccggcagcggcaagcctggcagcggcga gggcagcaccaagggcgaggtgaagctgcaggaaagcggccctggcctggtggcccccagccagagcctgagcgtgacctgca ccgtgagcggcgtgagcctgcccgactacggcgtgagctggatccggcagccccccaggaagggcctggaatggctgggcgtga tctggggcagcgagaccacctactacaacagcgccctgaagagccggctgaccatcatcaaggacaacagcaagagccaggtgtt cctgaagatgaacagcctgcagaccgacgacaccgccatctactactgcgccaagcactactactacggcggcagctacgccatgg actactggggccagggcaccagcgtgaccgtgagcagc). In some alternatives, the scFv comprises an

amino acid sequence set forth in SEQ ID NO: 43 (MLLLVTSLLLCELPHPAFLLIPDIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWY QQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLP YTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVSGVS LPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSL QTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 43. some alternatives, the scFv comprises a B7H3 (hBRCA84D) scFv nucleotide sequence. In some alternatives, the scFv binds specifically to the B7-H3 receptor. In some alternatives, the scFv comprises the L1CAM (CE7) scFv nucleotide sequence. In some alternatives, the scFv is specific for the epitope, CE7 epitope, of L1CAM. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 50

(atgctgctgctggtgaccagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggtgcagctgcagcagcct ggcgccgagctggtgaagccaggcgccagcgtgaagctgtcctgcaaggccagcggctacaccttcaccggctactggatgcact gggtgaagcagagacccggccacggcctggaatggatcggcgagatcaaccccagcaacggccggaccaactacaacgagcgg ttcaagagcaaggccaccctgaccgtggacaagagcagcaccaccgccttcatgcagctgtccggcctgaccagcgaggacagcg ccgtgtacttctgcgccagggactactacggcaccagctacaacttcgactactggggccagggcaccacactgaccgtgagcagc ggcggaggggctctggcggcggaggatctgggggaggggcagcgacatccagatgacccagagcagcagcagcttcagcg tgagcctgggcgaccgggtgaccatcacctgtaaggccaacgaggacatcaacaaccggctggcctggtatcagcagacccccgg caacagccccaggctgctgatcagcggcgccaccaacctggtgaccggcgtgcccagccggtttagcggcagcggctccggcaa ggactacaccctgaccatcacaagcctgcaggccgaggacttcgccacctactactgccagcagtactggtccacccccttcaccttc ggcagcggcaccgagctggaaatcaaa). In some alternatives, the scFv comprises the L1CAM (CE7) scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 51 (MLLLVTSLLLCELPHPAFLLIPQVQLQQPGAELVKPGASVKLSCKASGYTFTGYWM HWVKQRPGHGLEWIGEINPSNGRTNYNERFKSKATLTVDKSSTTAFMQLSGLTSEDS AVYFCARDYYGTSYNFDYWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSSSSFS VSLGDRVTITCKANEDINNRLAWYQQTPGNSPRLLISGATNLVTGVPSRFSGSGSGK DYTLTITSLQAEDFATYYCQQYWSTPFTFGSGTELEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the

amino acid sequence of SEQ ID NO: 51. In some alternatives, the scFv is encoded by the EGFR (cetuximab) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 52 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggtgcagctgaaacagagcg gcccgggcctggtgcagccgagccagagcctgagcattacctgcaccgtgagcggctttagcctgaccaactatggcgtgcattgg gtgcgccagagcccgggcaaaggcctggaatggctgggcgtgatttggagcggcggcaacaccgattataacaccccgtttacca gccgcctgagcattaacaaagataacagcaaaagccaggtgtttttttaaaatgaacagcctgcagagcaacgataccgcgatttattat tgcgcgcgcgcgctgacctattatgattatgaatttgcgtattggggccagggcaccctggtgaccgtgagcgcgggcggcggcgg cagcggcggcggcggcagcggcggcggcggcagcgatattctgctgacccagagcccggtgattctgagcgtgagcccgggcg aacgcgtgagctttagctgccgcgcgagccagagcattggcaccaacattcattggtatcagcagcgcaccaacggcagcccgcgc ctgctgattaaatatgcgagcgaaagcattagcggcattccgagccgctttagcggcagcggcagcggcaccgattttaccctgagc attaacagcgtggaaagcgaagatattgcggattattattgccagcagaacaacaactggccgaccacctttggcgcgggcaccaaa ctggaactgaaacgcacc). In some alternatives, the scFv comprises the EGFR scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 53 (MLLLVTSLLLCELPHPAFLLIPQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHW VRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIY YCARALTYYDYEFAYWGQGTLVTVSAGGGGSGGGGSGGGGSDILLTQSPVILSVSP GERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSI NSVESEDIADYYCQQNNNWPTTFGAGTKLELKRT). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 53. In some alternatives, the scFv comprises the EGFRVIII (806) scFv nucleotide sequence. In some alternatives, the scFv is specific for EGFR. In some alternatives, the scFv is encoded by the EphA2 (2A4) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 56. In some alternatives, the scFv is encoded by the EpHA2 (4H5) scFv nucleotide sequence. In some alternatives, the scFv is encoded by the nucleic acid sequence set forth in SEQ ID NO: 58. In some alternatives, the scFv is encoded by a FITC (E2) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 60. In some alternatives, the scFv is encoded by an IL13Ra2 (hu08) VhVl scFv nucleotide

sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 68. In some alternatives, the scFv comprises an IL13Ra2 hu08 VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 69 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFSRNGMS WVRQAPGKGLEWVATVSSGGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARQGTTALATRFFDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSS LSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIYSASYRSTGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQHHYSAPWTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 69. In some alternatives, the scFv is encoded by an IL13Ra2 (hu07) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 70 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatattcagatgacccagagccc gagcagcctgagcgcgagcgtgggcgatcgcgtgaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggt atcagcagaaaccgggcaaagcgccgaaactgctgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcgg cagcggcagcggcaccgattttaccctgaccattagcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgca gcccgctgaccttggcggcggcaccaaagtggaaattaaaggtggtggtggttctggcggcggcggctccggtggtggtggttctg aagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacct ttaccaaatatggcgtgcattgggtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagca ccgattataacagcgcgctgatgagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgc gcgcggaagataccgcggtgtattattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtg agcagcgaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 71 (MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCTASLSVSSTYLHWY QQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCHQYHRSP LTFGGGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFT KYGVHWVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARDHRDAMDYWGQGTLVTVSSESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the

amino acid sequence of SEQ ID NO: 71. In some alternatives, the scFv is encoded by the IL13Ra2 (hu07) VhVl scFv nucleotide sequence. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 72 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagaagtgcagctggtggaaagcg gcggcggcctggtgcagccgggcggcagcctgcgcctgagctgcgcggcgagcggctttacctttaccaaatatggcgtgcattgg gtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgaaatgggcgggcggcagcaccgattataacagcgcgctgat gagccgctttaccattagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgcgcgcggaagataccgcggtgt attattgcgcgcgcgatcatcgcgatgcgatggattattggggccagggcaccctggtgaccgtgagcagcggtggtggtggttctg gcggcggcggctccggtggtggtggttctgatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatcgcgt gaccattacctgcaccgcgagcctgagcgtgagcagcacctatctgcattggtatcagcagaaaccgggcaaagcgccgaaactgc tgatttatagcaccagcaacctggcgagcggcgtgccgagccgctttagcggcagcggcagcggcaccgattttaccctgaccatta gcagcctgcagccggaagattttgcgacctattattgccatcagtatcatcgcagcccgctgacctttggcggcggcaccaaagtgga aattaaagaatctaagta). In some alternatives, the scFv comprises an IL13Ra2 (hu07) VhVl scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 73 (MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVQPGGSLRLSCAASGFTFTKYGVH WVRQAPGKGLEWVAVKWAGGSTDYNSALMSRFTISRDNAKNSLYLQMNSLRAED TAVYYCARDHRDAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCTASLSVSSTYLHWYQQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCHQYHRSPLTFGGGTKVEIKESK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 73. In some alternatives, the antibody or portion thereof or scFv is encoded by the Anti-IL13Ra2 (IL13 zetakine) nucleotide sequence. In some alternatives, the antibody or portion thereof or scFv is encoded by a sequence set forth in SEQ ID NO: 74 (atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccaggccctgtgcctccctctacagcc ctcaggtacctcattgaggagctggtcaacatcacccagaaccagaaggctccgctctgcaatggcagcatggtatggagcatcaac ctgacagctggcatgtactgtgcagccctggaatccctgatcaacgtgtcaggctgcagtgccatcgagaagacccagaggatgctg agcggattctgcccgcacaaggtctcagctgggcagttttccagcttgcatgtccgagacaccaaaatcgaggtggcccagtttgtaa aggacctgctcttacatttaaagaaacttttcgcgagggacggttcaa). In some alternatives, the antibody or portion thereof or scFv comprises an Anti-IL13Ra2 (IL13 zetakine) amino acid sequence. In

some alternatives, the antibody or portion thereof or scFv comprises an amino acid sequence set forth in SEQ ID NO: 75 (MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSI NLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQ FVKDLLLHLKKLFREGRF). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 75. In some alternatives, the scFv is encoded by an oaGD2 (8B6) VlVh scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 76

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagatgttgtgatgacccaaactcca ctctccctgcctgtcagtcttggagatcaagcctcaatctcttgcagatctagtcagagccttctaaaaaataatggaaacacctttttaca ttggtacctgcagaagtcaggccagtctccaaagctccttatctacaaagtttccaaccgactttctggggtcccagacaggttcagtgg cagtggatcagggacatatttcacactcaagatcagcagagtggaggctgaggatctgggagtttatttctgctctcaaagtacacatat tccgtacacattcggaggggggaccaagctcgagctgaaacgaggcggaggggctctggcggcggaggatctgggggagggg gcagcgaggtgaaactggtggagtctggaggaggcttggtgctgcctggggattctctgagactctcctgtgcaacttctgagttcac cttcactgattactacatgacttgggtccgccagcctccaagaaaggcacttgagtggttgggttttattagaaacagagctaatggttac acaacagagtacaatccatctgtgaagggtcggttcaccatttccagagataattcccaaagcatcctctatcttcaaatgaacaccctg agaactgaggacagtgccacttattactgtgcaagagtctctaactgggcctttgactactggggccaaggcaccactctcacagtctc ctca). In some alternatives, the scFv comprises the oaGD2 (8B6) VlVh scFv amino acid sequence. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 77 (MLLLVTSLLLCELPHPAFLLIPDVVMTQTPLSLPVSLGDQASISCRSSQSLLKNNGNT FLHWYLQKSGQSPKLLIYKVSNRLSGVPDRFSGSGSGTYFTLKISRVEAEDLGVYFCS QSTHIPYTFGGGTKLELKRGGGGSGGGGSGGGGSEVKLVESGGGLVLPGDSLRLSCA TSEFTFTDYYMTWVRQPPRKALEWLGFIRNRANGYTTEYNPSVKGRFTISRDNSQSIL YLQMNTLRTEDSATYYCARVSNWAFDYWGQGTTLTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 77. In some alternatives, the scFv is encoded by an ROR1 (R12) scFv nucleotide sequence. In some alternatives, the scFv is encoded by a sequence set forth in SEQ ID NO: 78 (atgctgctgctggtgacaagcctgctgctgtgcgagctgccccaccccgcctttctgctgatcccccaggaacagctcgtcgaaagc

ggcggcagactggtgacacctggcggcagcctgaccctgagctgcaaggccagcggcttcgacttcagcgcctactacatgagctg ggtccgccaggcccctggcaagggactggaatggatcgccaccatctaccccagcagcggcaagacctactacgccacctgggtg aacggacggttcaccatctccagcgacaacgcccagaacaccgtggacctgcagatgaacagcctgacagccgccgaccgggcc acctacttttgcgccagagacagctacgccgacgacggcgccctgttcaacatctggggccctggcaccctggtgacaatctctagc ggcggaggcggatctggtggcggaggaagtggcggcggaggatctgagctggtgctgacccagagcccctctgtgtctgctgccc tgggaagccctgccaagatcacctgtaccctgagcagcgcccacaagaccgacaccatcgactggtatcagcagctgcagggcga ggcccccagatacctgatgcaggtgcagagcgacggcagctacaccaagaggccaggcgtgcccgaccggttcagcggatctag ctctggcgccgaccgctacctgatcatccccagcgtgcaggccgatgacgaggccgattactactgtggcgccgactacatcggcg gctacgtgttcggcggaggcacccagctgaccgtgaccggc). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 79 (ROR1 (R12) scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQEQLVESGGRLVTPGGSLTLSCKASGFDFSAYYMSW VRQAPGKGLEWIATIYPSSGKTYYATWVNGRFTISSDNAQNTVDLQMNSLTAADRA TYFCARDSYADDGALFNIWGPGTLVTISSGGGGSGGGGSGGGGSELVLTQSPSVSAA LGSPAKITCTLSSAHKTDTIDWYQQLQGEAPRYLMQVQSDGSYTKRPGVPDRFSGSS SGADRYLIIPSVQADDEADYYCGADYIGGYVFGGGTQLTVTG). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 79. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 80 (CD33 (h2H12) VhVl scFv nucleotide sequence

(atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccacaggttcagctggtgcagtctgga gctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggttacacctttaccaattatgatataaattgggtgag acaggcccctggacaagggcttgagtggattggatggatttatcctggagatggtagtaccaaatataatgagaaattcaaggccaag gctaccctgacagctgacacatccaccagcacagcctacatggagctgaggagcctgagatctgatgacacagctgtgtattactgtg cttctggatatgaagatgctatggactactgggggcaagggaccacagtcacagtctcctca). In some alternatives, the scFv is specific for CD33. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 81 (CD33 (h2H12) VhVl scFv amino acid sequence; MLLLVTSLLLCELPHPAFLLIPQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYDIN WVRQAPGQGLEWIGWIYPGDGSTKYNEKFKAKATLTADTSTSTAYMELRSLRSDDT AVYYCASGYEDAMDYWGQGTTVTVSS). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 81. In some alternatives, the scFv is encoded by a sequence set forth in SEQ

ID NO: 82 (CD33 (h2H12) VlVh scFv nucleotide sequence: atgcttctcctggtgacaagccttctgctctgtgagttaccacacccagcattcctcctgatcccagacatccagatgacccagtctccat cctcactgtctgcatctgtaggagacagagtcaccatcaattgtaaggctagtcaggacattaatagctatttgagctggtttcagcaga aaccagggaaagcccctaagaccctgatctatagagcaaatagattggtagatggggtcccatcaaggttctctggcagtggatctgg gcaagattatactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgcttgcagtatgatgagtttcctctcacatttgg aggagggaccaaggtggagatcaaa). In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 83 (CD33 (h2H12) VlVh scFv amino acid sequence: MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTINCKASQDINSYLSWFQ QKPGKAPKTLIYRANRLVDGVPSRFSGSGSGQDYTLTISSLQPEDFATYYCLQYDEFP LTFGGGTKVEIK). In some alternatives, the scFv is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 83. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 84. In some alternatives, the scFv is encoded by a nucleic acid sequence set forth in SEQ ID NO: 86. In some alternatives, the scFv comprises an amino acid sequence set forth in SEQ ID NO: 87. In some alternatives, the spacer is encoded by the nucleic acid sequence set forth in SEQ ID NO: 102 (IgG4 hinge nucleotide sequence: gagagcaagtacggaccgccctgccccccttgccct). In some alternatives, the spacer comprises an amino acid sequence set forth in SEQ ID NO: 103 (IgG4 hinge amino acid sequence: ESKYGPPCPPCP). In some alternatives, the spacer is encoded by a nucleic acid sequence comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 103. In some alternatives, the spacer is encoded by a nucleic acid sequence set forth in SEQ ID NO: 104. In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives, HEA3 comprises two amino acid mutations, wherein the sequence is encoded by a sequence set forth in SEQ ID NO: 122 (atggtgtccaagctgtcccagctgcagacagaactgctggcagcactgctggaaagcggcctgagcaaagaggccctgattcagg cactcggcgaacctggaccttatctgctcgctggcgaaggccctctggataagggcgagagctgtggcggaggaagaggagagct ggccgagctgcctaacggcctgggcgagacaagaggcagcgaggacgagacagacgacgacggcgaggacttcacccccccc

atcctgaaagagctggaaaacctgagccccgaggaagccgcccaccagaaagccgtggtggagacactgctgcaggaagatccc
tggcgggtcgccaagatggtcaagagctacctgcagcagcacaacatcccccagcgggaggtggtggacaccaccggcctgaac
cagagccacctgagccagcacctgaacaagggcacccccatgaaaacccagaagagagccgccctgtacacttggtacgtgcgg
aagcagagagaggtggcccagcagtttacacacgccggccagggcggcctgatcgaggaacctaccggcgacgagctgcccac
caagaagggcagacggaaccggtttaagtggggccctgcatctcagcagatcctgttccaggcctacgagcggcagaagaacccc
agcaaagaggaacgggagacactggtggaagagtgcaaccgggccgagtgcatccagagaggcgtgagcccttctcaggctcag
ggcctcggcagcaatctggtcaccgaagtgcgggtgtacaattggttcgccaaccggcggaaagaggaagccttccggcacaagct
gtctgctggcgatatgagagccgccaacctgtggcccagccccctgatgatcaagcggagcaagaagaacagcctggccctgagc
ctgaccgccgatcagatggtgtccgctctgctggacgccgagcccctatcctgtacagcgagtacgaccccaccagacccttcagc
gaggccagcatgatgggcctgctgaccaacctggccgaccgggagctggtgcacatgatcaactgggccaagcgggtgcccggc
ttcgtggacctgaccctgcacgaccaggtccacctgctggaatgtgcctggctggaaatcctgatgatcggcctcgtgtggagaagc
atggaacaccccggcaagctgctgttcgcccccaacctgctcctggaccggaaccagggaaagtgcgtggagggcatggtggaga
tcttcgacatgctgctggccacctccagccggttccggatgatgaacctgcagggcgaggaattcgtgtgcctgaagtccatcatcct
gctgaacagcggcgtgtacaccttcctgtcatccaccctgaagtccctggaagagaaggaccacatccaccgggtgctggacaaga
tcaccgacaccctgatccacctgatggccaaggctggcctgacactccagcagcagcaccagagactggcccagctgctgctgatc
ctgagccacatccggcacatgagcaacaagcggatggaacacctgtacagcatgaagtgcaagaacgtggtgcccctgtacgacct
gctgctcgagatgctggatgcccacagactgcacgcccctacaagcagaggcggagccagcgtggaggaaaccgaccagtctca
cctggccaccgccggcagcacaagcagccacagcctgcagaagtactacatcaccggcgaggccgagggattccctgccaccgt
ggagttccagtacctgcccgacaccgacgaccggcaccggatcgaggaaaagcggaagcggacctacgagacattccagagcat
catgaagaagtccccccttcagcggccccaccgatcccagacccccccctagaagaatcgccgtgcccagcagatctagcgccagc
gtgcccaagcctgccccccagccctacccctttcaccagcagcctgagcaccatcaactacgacgagttccctaccatggtgttcccca
gcggccagatctctcaggcctctgctctggcacctgctccacctcaggtgctgcctcaggcccctgctccagccccagcccctgccat
ggtgtctgcactggcccaggctccagctcctgtgcctgtgctggcccctggacctcctcaggctgtggcccctcctgcccctaaacct
acccaggccggggagggaacactgtctgaggccctgctgcagctccagttcgacgacgaggatctgggagcactgctgggcaata
gcaccgaccccgccgtgtttaccgacctggcctccgtggacaacagcgagttccagcagctcctcaaccagggcatccctgtcgcc
ccacacaccaccgagcccatgctgatggaataccccgaggccatcaccagactggtcacaggcgcccagaggcctccagatccag
caccagctccactgggagcccctggcctgcctaatgggctgctgtctggcgacgaggacttcgagagcattgccgacatggacttca
gcgccctgctgtcccagatcagcagc). In some alternatives, the HEA3 comprises an amino acid sequence set forth in SEQ ID NO: 121 (MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGEL AELPNGLGETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWR

VAKMVKSYLQQHNIPQREVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVR
KQREVAQQFTHAGQGGLIEEPTGDELPTKKGRRNRFKWGPASQQILFQAYERQKNP
SKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVTEVRVYNWFANRRKEEAFRHK
LSAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLDAEPPILYSEYDPTRPF
SEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLV
WRSMEHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVC
LKSIILLNSGVYTFLSSTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLA
QLLLILSHIRHMSNKRMEHLYSMKCKNVVPLYDLLLEMLDAHRLHAPTSRGGASVE
ETDQSHLATAGSTSSHSLQKYYITGEAEGFPATVEFQYLPDTDDRHRIEEKRKRTYET
FQSIMKKSPFSGPTDPRPPPRRIAVPSRSSASVPKPAPQPYPFTSSLSTINYDEFPTMVFP
SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQAVAPPAP
KPTQAGEGTLSEALLQLQFDDEDLGALLGNSTDPAVFTDLASVDNSEFQQLLNQGIP
VAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAPGLPNGLLSGDEDFESIADM
DFSALLSQISS). This sequence comprises the sequence of HEA3 containing two point mutations (K310Q and S536E, positions in the RelA protein) in the p65 domain that enhance transcriptional activity. This is referred to as HEA3(p65/S536E/K310Q). K310Q in RelA corresponds to position 621 in HEA3; S536E corresponds to position 846 in HEA3. In some alternatives, a system for inducible expression of a chimeric antigen receptor in cells is provided. In some alternatives, the transgene encodes a polypeptide that regulates apoptosis. In some alternatives, genes that inhibit apoptosis include, for example, Bcl2, and/or CA-Akt. In some alternatives, the polypeptide is Bcl2 or CA-Akt. In some alternatives, genes that inhibit apoptosis include, for example, Survivin, Bcl2, CA-Akt, and/or dnCaspase3. In some alternatives, the polypeptide is Survivin, Bcl2, or CA-Akt and/or dnCaspase 3. In some alternatives, Survivin is encoded by a sequence set forth in SEQ ID NO: 124 (Atgggtgccccgacgttgccccctgcctggcagccctttctcaaggaccaccgcatctctacattcaagaactggcccttcttggag
ggctgcgcctgcaccccggagcggatggccgaggctggcttcatccactgccccactgagaacgagccagacttggcccagtgttt
cttctgcttcaaggagctggaaggctgggagccagatgacgaccccatagaggaacataaaaagcattcgtccggttgcgctttccttt
ctgtcaagaagcagtttgaagaattaacccttggtgaatttttgaaactggacagagaaagagccaagaacaaaattgcaaaggaaac
caacaataagaagaaagaatttgaggaaactgtgaagaaagtgcgccgtgccatcgagcagctggctgcaatggat). In some alternatives, Survivin comprises the amino acid sequence set forth in SEQ ID NO: 123 (MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEPDLAQC

FFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKLDRERAKNKIAK ETNNKKKEFEETVKKVRRAIEQLAAMD).

Vector construction and preparation of dual packaged lentivirus.

[0309] An inducible lentiviral vector encoding constitutively expressed drug-inducible transcription factors was constructed. The constructs encoded HEA3 single RelA variants, HEA4 single RelA variants, HEA4 double RelA variants (SEQ ID NO: 12-21) wild type HEA3, or wild type HEA4 and a ZsGreen fluorescent reporter.

[0310] A conditional lentiviral vector encoding 7xHBD/mE1B-ZsGreen- epHIV7 was constructed. The synthetic promoter 7xHBD/mE1B was constructed by combining seven minimal Hepatocyte Nuclear Factor 1-alpha (HNF1α) binding sites cloned from the human albumin promoter and the E1B TATA box. In this way, only in the presence of tamoxifen does binding of HEA3 or HEA4 to 7xHBD/mE1B promoter induce the "ON" state of transgene expression.

[0311] The transcriptional regulator, HEA3, is a chimeric transcription factor composed of human subunits including the N-terminal DNA binding domain of Hepatocyte Nuclear Factor 1-alpha (HNF-1α) fused in frame to the mutant tamoxifen-specific ligand binding domain of the estrogen receptor ligand binding domain (ER-LBD), that is in turn fused to the p65 activation domain of NF-κβ (p65). In the absence of tamoxifen, HEA3 is excluded from the nucleus by binding of cytosolic heat-shock protein 90 (HSP90) to the tamoxifen binding active site and transgene expression is in the "OFF" state. Nanomolar concentrations of cytosolic tamoxifen actively outcompete HSP90 for ER-LBD binding, resulting in HEA3 translocation to the nucleus. Upon nuclear translocation, HEA3 is readily available to bind its restricted synthetic promoter. Transcriptional responsiveness to HEA3 in the presence of tamoxifen is achieved when transgenes are placed behind an HEA3 responsive synthetic promoter (7xHBD/mE1B). In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the transgene encodes a chimeric antigen receptor. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120

or any percent sequence identity in between a range defined by any two aforementioned values.

[0312] The transcriptional regulator, HEA4, is a chimeric transcription factor composed of human subunits including the N-terminal DNA binding domain of Hepatocyte Nuclear Factor 1-alpha (HNF-1α) fused in frame to the mutant tamoxifen-specific ligand binding domain of the estrogen receptor ligand binding domain (ER-LBD) containing 3 amino acid substitutions that abolish sensitivity to estradiol, that is in turn fused to the p65 activation domain of NF-κβ (p65). Single or double mutations in the p65 activation domain have been constructed to enhance transcriptional activity. In the absence of tamoxifen, HEA4 is excluded from the nucleus by binding of cytosolic heat-shock protein 90 (HSP90) to the tamoxifen binding active site and transgene expression is in the "OFF" state. Nanomolar concentrations of cytosolic tamoxifen actively outcompete HSP90 for ER-LBD binding, resulting in HEA4 translocation to the nucleus. Upon nuclear translocation, HEA4 is readily available to bind its restricted synthetic promoter. Transcriptional responsiveness to HEA4 in the presence of tamoxifen is achieved when transgenes are placed behind an HEA4 responsive synthetic promoter (7xHBD/mE1B). In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values. In some alternatives, the transgene encodes a chimeric antigen receptor.

[0313] The synthetic promoter 7xHBD/mE1B consists of seven minimal Hepatocyte Nuclear Factor -1 (HNF-1α) binding sites cloned from the human albumin promoter and the mE1B promoter TATA box. In this way, only in the presence of tamoxifen does binding of HEA3 or HEA4 to 7xHBD/mE1B promoter induce the "ON" state of transgene expression. In some alternatives, a DNA spacer is between the inducible promoter and the transgene. In some alternatives, the DNA spacer comprises a sequence set forth in SEQ ID NO: 120 (SEQ ID NO: 120; gctagcgtttaaacttaagcttggtaccgagctcggatccgccacc). In some alternatives, the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range

defined by any two aforementioned values. In some alternatives, the transgene encodes a chimeric antigen receptor.

[0314] The nucleic acid sequences encoding the chimeric transcription factors were constructed under the control of an EF1a constitutive promoter. The nucleic acid sequences encoding chimeric transcription factors were linked with sequences encoding the self-cleaving T2A sequence and a marker sequence EGFRt and cloned into an epHIV7.2 lentiviral backbone.

[0315] Lentivirus housing constitutive chimeric transcription factors and the inducible 7xHBD/mE1B-ZsGreen were produced in 293T cells co-transfected at a 1:2 (HEA3 or HEA4:7xHBD/mE1B) molar ratio with packaging vectors pCHGP-2, pCMV-Rev2 and pCMV-G using Lipofectamine 2000 (Life Technologies). Medium was changed 16 hours after transfection and virus was collected after 72 hours. Virus was concentrated at 24,500 rpm for 1 hour and 34 minutes at 4C.

Generation of Jurkat lines expressing ZsGreen when induced with tamoxifen.

[0316] Jurkat cells were transduced with lentiviral supernatant (MOI $\geq$ 3) supplemented with 1 μg/mL protamine sulfate (Seattle Children's Hospital Pharmacy). Transduced Jurkat cells were expanded in RPMI, 10% FBS and 2 mM L-glutamine. 10-30 days following transduction, EGFRt+ cells were enriched using biotinylated cetuximab and anti-biotin magnetic microbeads (Miltenyi). Cells were cultured in RPMI, 10% FBS and 2 mM L-glutamine until use in cellular assays.

Schematic of dual-packaged lentiviral constructs housing the constitutively expressed drug-inducible transcription factors

[0317] Jurkat cells expressing HEA3 (Fig. 1A) or (Fig. 1B) HEA4 single mutant RelA variants (S536E or K310Q or WT [wild-type]), and a ZsGreen fluorescent reporter vectors were constructed.

Characterization of "ON" and "OFF" states of HEA3 and HEA4 single mutant RelA variants

[0318] Jurkat cells were seeded at 5.0E5 cells/mL in the presence or absence of 500 nM 4-OHT. After 24 hours, cells were collected and stained with biotinylated cetuximab and Streptavidin-APC in HBSS containing 2% FBS and 0.1% NaN_3 and fixed in PBS with paraformaldehyde. EGFRt and ZsGreen reporter expression was obtained on a MACSQuant (Miltenyi). Data was analyzed using FlowJo Version 10. ZsGreen reporter expression in

Jurkat cells expressing (Fig. 1C) HEA3 or (Fig. 1D) HEA4 single mutant RelA (S536E or K310Q)_variants following 24 hours of culture with 500 nM 4-OHT are shown.

[0319] Characterization of 4-OHT Dose Response of HEA3 and HEA4 Single Mutant RelA Variants

[0320] Jurkat cells expressing (Fig. 1A) HEA3 or (Fig. 1B) HEA4 single mutant RelA variants (S536E or K310Q or WT [wild-type]), and a ZsGreen fluorescent reporter vectors were seeded at 5.0E5 cells/mL with increasing doses of 4-OHT. After 24 hours, cells were collected and stained with biotinylated cetuximab and Streptavidin-APC in HBSS containing 2% FBS and 0.1% and fixed in PBS with paraformaldehyde. EGFRt and ZsGreen reporter expression was obtained on a MACSQuant (Miltenyi). Data was analyzed using FlowJo Version 10. 4-OHT dose response are shown: Percentage of EGFRt+ZsGreen+ cells and ZsGreen median fluorescent intensity of (Fig. 1E) HEA3 or (Fig. 1F) HEA4 RelA variant expressing Jurkat cells.

Schematic of dual-packaged lentiviral constructs housing the constitutively expressed drug-inducible transcription factors

[0321] Jurkat cells expressing an HEA4 (Fig. 2A) double mutant RelA (S536E/ K310Q) variant or a CMP8-responsive (Fig. 2B) HEA3 single mutant RelA (S536E) variant and a ZsGreen fluorescent reporter vector were constructed.

[0322] Characterization of "ON" and "OFF" States of HEA4 Double Mutant RelA Variants and CMP8-Responsive HEA3 Single Mutant RelA Variants

[0323] Jurkat cells were seeded at 5.0E5 cells/mL in the presence or absence of 500 nM 4-OHT (Fig. 2C) or CMP8 (Fig. 2D). After 24 hours, cells were collected and stained with biotinylated cetuximab and Streptavidin-APC in HBSS containing 2% FBS and 0.1% and fixed in PBS with paraformaldehyde. EGFRt and ZsGreen reporter expression was obtained on a MACSQuant (Miltenyi). Data was analyzed using FlowJo Version 10. ZsGreen reporter expression in Jurkat cells expressing (Fig. 2C) the HEA4 double mutant RelA (S536E/K310Q) variant or (Fig. 2D) CMP8-responsive HEA3 single mutant RelA (S536E) variant following 24 hours of culture with 500 nM 4-OHT or 500 nM CMP8 are shown.

Characterization of 4-OHT dose response of HEA4 double mutant RelA variants and CMP8-responsive HEA3 single mutant RelA variants

[0324] Jurkat cells expressing (Fig. 2A) HEA4 double mutant RelA variants (S536E/K310Q) or (Fig. 2B) CMP8-responsive HEA3 single mutant RelA variants, and a ZsGreen fluorescent reporter vectors were seeded at Jurkat cells were seeded at 5.0E5 cells/mL with increasing doses of 4-OHT or CMP8. After 24 hours, cells were collected and stained with biotinylated cetuximab and Streptavidin-APC in HBSS containing 2% FBS and 0.1% and fixed in PBS with paraformaldehyde. EGFRt and ZsGreen reporter expression was obtained on a MACSQuant (Miltenyi). Data was analyzed using FlowJo Version 10. 4-OHT dose response are shown: Percentage of EGFRt+ZsGreen+ cells and ZsGreen median fluorescent intensity of (Fig. 2E) the HEA4 double mutant RelA (S536E/K310Q) variant or (Fig. 2F) CMP8-responsive HEA3 single mutant RelA (S536E) variant expressing Jurkat cells.

Lentiviral vectors comprising a DNA spacer.

[0325] Jurkat cells expressing an HEA4 double mutant RelA (S536E/ K310Q) variant or a CMP8-responsive HEA3 single mutant RelA (S536E) variant and a ZsGreen fluorescent reporter vector were constructed. For comparison of expression levels, Jurkat cells expressing an HEA4 double mutant RelA (S536E/ K310Q) variant comprising a DNA spacer between the promoter and transgene or a CMP8-responsive HEA3 single mutant RelA (S536E) variant comprising a DNA spacer between the promoter and transgene and a ZsGreen fluorescent reporter vector were also constructed.

[0326] Jurkat cells were seeded at 5.0E5 cells/mL in the presence or absence of 500 nM 4-OHT (Fig. 2C) or CMP8. After 24 hours, cells were collected and stained with biotinylated cetuximab and Streptavidin-APC in HBSS containing 2% FBS and 0.1% and fixed in PBS with paraformaldehyde. EGFRt and ZsGreen reporter expression was obtained on a MACSQuant (Miltenyi). Data was analyzed using FlowJo Version 10. ZsGreen reporter expression in Jurkat cells expressing the HEA4 double mutant RelA (S536E/K310Q) variant or CMP8-responsive HEA3 single mutant RelA (S536E) variant following 24 hours of culture with 500 nM 4-OHT or 500 nM CMP8 were compared to the expression of Jurkat cells expressing the HEA4 double mutant RelA (S536E/K310Q) variant that had the DNA spacer and the CMP8-responsive HEA3 single mutant RelA (S536E) variant that had the DNA spacer following 24 hours of culture with 500 nM 4-OHT or 500 nM CMP8. It is expected that the expression of the transgenes increased 1.5 to 2.0 fold as compared to the

vectors that lacked the DNA spacer between the promoters and the transgene. This is also dependent on the transgene. The DNA spacer comprised the sequence set forth in SEQ ID NO: 120.

Additional Methods

Vector construction and preparation of dual packaged lentivirus.

[0327] An inducible lentiviral vector encoding constitutively expressed drug inducible transcription factors was constructed. The constructs encoded the HEA4 (p65/S536E/K310Q) double mutant RelA variant (SEQ ID NO: 7) and an eGFP:ffluc reporter. In some cases, constructs encoded the HEA4(p65/S536E/K310Q) double mutant RelA variant and Survivin or CCR(CD122).

[0328] The conditional lentiviral vectors (7xHBD/mE1B_eGFP:ffluc_epHIV7.2, 7xHBD/mE1B_Survivin-T2A-Her2tG_epHIV7.2, and 7xHBD/mE1B_CCR(CD122)-T2A-Her2tG_epHIV7.2) were constructed. The synthetic promoter 7xHBD/mE1B was constructed by combining seven minimal Hepatocyte Nuclear Factor1-alpha (HNF-1α) binding sites cloned from the human albumin promoter and the E1B TATA box. In this way, only in the presence of tamoxifen does binding of HEA3 or HEA4 to 7xHBD/mE1B promoter induce the "ON" state of transgene expression

[0329] The transcriptional regulator, HEA4(p65/S536E/K310Q), is a chimeric transcription factor composed of human subunits including the N-terminal DNA binding domain of Hepatocyte Nuclear Factor 1-alpha (HNF-1α) fused in frame to the mutant tamoxifen-specific ligand binding domain of the estrogen receptor ligand binding domain (ER-LBD) containing 3 amino acid substitutions that abolish sensitivity to estradiol, that is in turn fused to the p65 activation domain of NF-κβ (p65). Two mutations (S536E/K310Q) were introduced into the p65 activation domain to enhance transcriptional activity. In the absence of tamoxifen, HEA4(p65/S536E/K310Q) is excluded from the nucleus by binding of cytosolic heat-shock protein 90 (HSP90) to the tamoxifen binding active site and transgene expression is in the "OFF" state. Nanomolar concentrations of cytosolic tamoxifen actively outcompete HSP90 for ER-LBD binding, resulting in HEA4(p65/S536E/K310Q) translocation to the nucleus. Upon nuclear translocation, HEA4(p65/S536E/K310Q) is readily available to bind its restricted synthetic promoter. Transcriptional responsiveness to

HEA4(p65/S536E/K310Q) in the presence of tamoxifen is achieved when transgenes are placed behind an HEA4(p65/S536E/K310Q) responsive synthetic promoter (7xHBD/mE1B). The synthetic promoter 7xHBD/mE1B consists of seven minimal Hepatocyte Nuclear Factor 1-alpha (HNF-1α) binding sites cloned from the human albumin promoter and the E1B promoter TATA box. In this way, only in the presence of tamoxifen does binding of HEA4(p65/S536E/K310Q) to 7xHBD/mE1B promoter induce the "ON" state of transgene expression.

[0330] The nucleic acid sequences encoding the chimeric transcription factors were constructed under the control of an EF1a constitutive promoter. The nucleic acid sequences encoding chimeric transcription factors were linked with sequences encoding the self-cleaving T2A sequence and a marker sequence EGFRt and cloned into an epHIV7.2 lentiviral backbone.

[0331] The nucleic acid sequences encoding Survivin or CCR(CD122) were linked with sequences encoding the self-cleaving T2A sequence and a marker sequence Her2tG and cloned into an epHIV7.2 lentiviral backbone.

[0332] Lentivirus housing the constitutive chimeric transcription factor and the inducible (Fig. 3A, 4A, 5A) 7xHBD/mE1B_eGFP:ffluc, (Fig. 6A) 7xHBD/mE1B_Survivin-T2A-Her2tG, or (Fig. 6B) 7xHBD/mE1B_CCR(CD122)-T2A-Her2tG were produced in 293T cells co-transfected at a 1:2 (HEA4(p65/S536E/K310Q):7xHBD/mE1B) molar ratio with packaging vectors pCHGP-2, pCMV-Rev2 and pCMV-G using Lipofectamine 2000 (Life Technologies). Medium was changed 16 hours after transfection and virus was collected after 72 hours. Virus was concentrated at 24,500 rpm for 1 hour and 34 minutes at 4C.

Generation of CD4+ and CD8+ T cells expressing eGFP:ffluc when induced with tamoxifen.

[0333] Human CD4+ and CD8+ T cells were isolated from PBMCs using CD4 and CD8 Microbeads (Miltenyi). CD4+ and CD8+ T cells were cultured separately for the entirety of the experiments. Immediately following isolation, CD4+ and CD8+ T cells were stimulated with Dynabeads Human T-Activator CD3/CD28 for T Cell Expansion (Life Technologies) at a 1:1 bead:cell ratio. CD4+ T cells were cultured with RPMI, 10% FBS, 2 mM L-glutamine, IL-7 (5 ng/mL), and IL-15 (0.5 ng/mL). CD8+ T cells were cultured with

RPMl, 10% FBS and 2 mM L-glutamine, IL-2 (50 U/mL), and IL-15 (0.5 ng/mL). Two days following isolation, CD4+ and CD8+ T cells were transduced with lentiviral supernatant (MOl 1.0) supplemented with 1 μg/mL protamine sulfate (Seattle Children's Hospital Pharmacy). 10-15 days following transduction, EGFRt+ cells were enriched using biotinylated cetuximab and anti-biotin magnetic microbeads (Miltenyi). 21 days following start of culture, T cells were expanded for 14 days via the Rapid Expansion Protocol using irradiated TM-LCLs, PBMCs, and anti-CD3 (OKT3) antibody (30 ng/mL). In some cases, T cells underwent a second expansion using the Rapid Expansion Protocol for an additional 14 days.

Schematic of dual-packaged lentiviral constructs housing the constitutively expressed drug-inducible transcription factors.

[0334] CD4+ and CD8+ T cells expressing (Fig. 3A, 4A, and 5A) HEA4(p65/S536E/K310) and an eGFP:ffluc reporter were constructed.

Expression of drug-inducible transcription factor confirmed by western blot.

[0335] 5.0e6 transduced and mock-transduced CD8+ T cells were collected. Cells were lysed with RIPA Buffer supplemented with protease inhibitors. 10 μg of protein was run on NuPAGE 4-12% Bis-Tris gel and transferred to nitrocellulose membrane. Membrane was blocked for 1 hour at room temperature and then probed with rabbit anti-p65 antibody (Cell Signaling) overnight at 4C. Membrane was washed and probed with goat anti-rabbit IR Dye 800 CW (LiCor). (Fig. 3B) Membrane was washed and imaged using Li-Cor Odyssey CLX Scanner to confirm expression of HEA4(p65/S536E/K310Q).

Expression of drug-inducible transcription factor and background level of eGFP confirmed by flow cytometry.

[0336] 1.0e6 transduced and mock-transduced CD8+ T cells were collected and stained with biotinylated cetuximab and Streptavidin-APC in HBSS containing 2% FBS and 0.1% NaN_3 and fixed in PBS with paraformaldehyde. (Fig. 3C) EGFRt and eGFP reporter expression was obtained on a MACSQuant (Miltenyi).

Characterization of "ON" and "OFF" states of HEA4(p65/S536E/K310Q) double mutant RelA variant in CD4+ and CD8+ T cells.

[0337] 1.0e5 transduced and mock-transduced CD4+ and CD8+ T cells were seeded in the presence or absence of 0 – 500 nM 4-OHT with or without Dynabeads (2:1 bead:cell ratio) or PMA (2μM)/Ionomycin (20 ng/mL) for 24 hours. Cells were harvested

and stained with biotinylated cetuximab and Streptavidin-APC in HBSS containing 2% FBS and 0.1% NaN_3. Cells were fixed in PBS with paraformaldehyde. EGFRt and eGFP reporter expression was obtained on a MACSQuant (Miltenyi). Data was analyzed using FlowJo Version 10. eGFP reporter expression in CD4+ and CD8+ T cells expressing (Fig. 4B) HEA4(S536E/K310Q) variants following 24 hours of culture with 0, 30, or 500 nM 4-OHT are shown.

4-OHT dose response of HEA4(S536E/K310Q) double mutant RelA variant in CD4+ and CD8+ T cells.

[0338] 1.0e5 CD4+ and CD8+ transduced or mock control T cells were seeded in the presence or absence of 0 – 500 nM 4-OHT with or without Dynabeads (2:1 bead:cell ratio) or PMA (2μM) /Ionomycin (20 ng/mL) for 24 hours. Cells were harvested and stained with biotinylated cetuximab and Streptavidin-APC in HBSS containing 2% FBS and 0.1% NaN_3. Cells were fixed in PBS with paraformaldehyde. EGFRt and eGFP reporter expression was obtained on a MACSQuant (Miltenyi). Data was analyzed using FlowJo Version 10. %EGFRt+eGFP+ (Fig. 5B) CD4+ and (Fig. 5C) CD8+ T cells and (Fig. 5D-5E) eGFP median fluorescence intensity following 24 hours of culture with 0 – 500 nM 4-OHT are shown.

Schematic of dual-packaged lentiviral constructs housing the constitutively expressed drug-inducible transcription factors.

[0339] Jurkat cells expressing HEA4(p65/S536E/K310) and (Fig. 6A) inducible 7xHBD/mE1B_Survivin-T2A-Her2tG or (Fig. 6B) inducible 7xHBD/mE1B_CCR(CD122) -T2A-Her2tG were constructed.

Generation of Jurkat cell lines expressing Survivin or CCR(CD122) when induced with tamoxifen.

[0340] Jurkat cells were transduced with lentiviral supernatant (MOI ≥ 3.0) supplemented with 1.0 μg/mL protamine sulfate (Seattle Children's Hospital Pharmacy). Jurkat cells were cultured with RPMI, 10% FBS and 2 mM L-glutamine.

"ON" state switching of HEA4(p65/S536E/K310Q) double mutant RelA variant and inducible Survivin or CCR(CD122) in Jurkat cells

[0341] Jurkat cells were seeded at 5.0e5 cells/mL in the presence or absence of 500 nM 4-OHT for 24 hours. Cells were harvested and stained with cetuximab-APC, biotinylated Herceptin, and Streptavidin-PE in HBSS containing 2% FBS and 0.1% NaN_3. Cells were fixed in PBS with paraformaldehyde. EGFRt and Her2tG expression was obtained

on a MACSQuant (Miltenyi). Data was analyzed using FlowJo Version 10. Her2tG expression in Jurkat cells expressing HEA4(S536E/K310Q) double mutant RelA variant and (Fig. 6C) inducible Survivin or (Fig. 6D) inducible CCR(CD122) following 24 hours of culture with 500 nM 4-OHT are shown.

[0342] The present invention has been described above with reference to specific alternatives. However, other alternatives than the above described are equally possible within the scope of the invention. Different method steps than those described above, may be provided within the scope of the invention. The different features and steps of the invention may be combined in other combinations than those described. The scope of the invention is only limited by the appended patent claims.

[0343] With respect to the use of plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity.

[0344] It will be understood by those of skill within the art that, in general, terms used herein, and especially in the appended claims (e.g., bodies of the appended claims) are generally intended as "open" terms (e.g., the term "including" should be interpreted as "including but not limited to," the term "having" should be interpreted as "having at least," the term "includes" should be interpreted as "includes but is not limited to," etc.).

[0345] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0346] Any of the features of an alternative of the first through eleventh aspects is applicable to all aspects and alternatives identified herein. Moreover, any of the features of an alternative of the first through eleventh aspects is independently combinable, partly or wholly with other alternatives described herein in any way, e.g., one, two, or three or more alternatives may be combinable in whole or in part. Further, any of the features of an alternative of the first through eleventh aspects may be made optional to other aspects or alternatives. Although described above in terms of various example alternatives and implementations, it should be understood that the various features, aspects and functionality

described in one or more of the individual alternatives are not limited in their applicability to the particular alternative with which they are described, but instead may be applied, alone or in various combinations, to one or more of the other alternatives of the present application, whether or not such alternatives are described and whether or not such features are presented as being a part of a described alternative. Thus, the breadth and scope of the present application should not be limited by any of the above-described example alternatives.

[0347] All references cited herein are incorporated herein by reference in their entirety. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material. To the extent publications and patents or patent applications incorporated by reference herein contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

WHAT IS CLAIMED IS:

1. A system for inducible expression of a chimeric antigen receptor in cells, the system comprising:

a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide that encodes a chimeric antigen receptor, which comprises a ligand binding domain that is specific for a ligand selected from the group consisting of a tumor specific molecule, a viral specific molecule, and any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte;

a second polynucleotide, which encodes a spacer, preferably an optimized polypeptide spacer;

a third polynucleotide, which encodes a transmembrane domain; and

a fourth polynucleotide, which encodes an intracellular signaling domain; and

b) a second nucleic acid comprising a second promoter that is operably linked to a nucleic acid encoding a transcriptional activator for the first promoter inducible by a drug, wherein the system is inducible by an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3.

2. The system of Claim 1, wherein the transcriptional activator is HEA3 or HEA4.

3. The system of Claim 2, wherein HEA3 is a variant of a wild type HEA3 transcription factor.

4. The system of Claim 2, wherein HEA4 is a variant of a wild type HEA4 transcription factor.

5. The system of any one of Claims 2-3, wherein HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and

wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand.

6. The system of any one of Claims 2-3, wherein HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug.

7. The system of Claim 2 or 4, wherein HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand.

8. The system of any one of Claims 2, 4 or 7, wherein HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug.

9. The system of any one of Claims 2-8, wherein the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand.

10. The system of any one of Claims 2, 3, 5, 6 or 9, wherein the variant of the wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121.

11. The system of any one of Claims 2, 3, 5, 6, 9 or 10, wherein the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122.

12. The system of any one of Claims 2, 4 or 7-9, wherein the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7.

13. The system of any one of Claims 2, 4, 7-9 or 12 wherein the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18.

14. The system of any one of Claims 1-13, wherein the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8.

15. The system of any one of Claims 1-14, wherein the first promoter comprises a nucleic acid sequence set forth in SEQ ID NO: 23.

16. The system of any one of Claims 1-15, wherein the drug induces a high expression of the chimeric antigen receptor, such as at a concentration of at least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of drug or a concentration that is within a range defined by any two of the aforementioned values, as compared to a wild type HEA3 or a wild type HEA4 chimeric transcription factor.

17. The system of any one of Claims 1-16, wherein the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero.

18. The system of Claim 17, wherein the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage amount for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor.

19. The system of Claim 18, wherein the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss.

20. The system of any one of Claims 1-19, wherein the signaling domain comprises a CD28, 4-1BB and/or CD3ζ domain.

21. The system of any one of Claims 1-20, wherein the second promoter is an inducible promoter.

22. The system of any one of Claims 1-20, wherein the second promoter is a constitutive promoter.

23. The system of Claim 22, wherein the second promoter is the EF1αp.

24. The system of any one of Claims 1-23, wherein the transcriptional activator comprises at least one amino acid sequence set forth in SEQ ID NO: 1-11 or 121.

25. The system of any one of Claims 1-24, wherein the transcriptional activator is encoded by at least one nucleic acid sequence set forth in SEQ ID NO: 12-22 or 122.

26. The system of any one of Claims 1-25, wherein the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector.

27. The system of Claim 26, wherein both vectors are packaged in a viral vector.

28. The system of Claim 27, wherein the viral vector is an adeno-associated virus or a lentivirus.

29. The system of any one of Claims 1-28, wherein the first nucleic acid further comprises a fifth polynucleotide that encodes a selectable marker.

30. The system of any one of Claims 1-29, wherein the second nucleic acid further comprises a sixth polynucleotide that encodes a selectable marker.

31. The system of Claim 29 or 30, wherein the selectable marker is EGFRt and/or HER2t.

32. The system of Claim 29 or 30, wherein the selectable marker confers drug resistance.

33. The system of any one of Claims 1-32, wherein the first nucleic acid further comprises a seventh polynucleotide that encodes a self-cleaving peptide.

34. The system of Claim 33, wherein the self-cleaving peptide comprises a P2A, T2A, E2A or F2A peptide.

35. The system of any one of Claims 1-34, wherein the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor.

36. The system of any one of Claims 1-35, wherein the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor.

37. The system of Claim 36, wherein the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor.

38. The system of any one of Claims 36 or 37, wherein the DNA spacer comprises a sequence set forth in SEQ ID NO: 120.

39. The system of any one of Claims 36-37, wherein the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values.

40. The system of any one of Claims 36-39, wherein the DNA spacer enhances gene expression of the chimeric antigen receptor.

41. A system for inducible expression of a gene that regulates a T cell function comprising:

a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a first polynucleotide, which encodes a cytokine, a chemokine receptor, a chimeric cytokine receptor, a polypeptide that regulates apoptosis, a polypeptide that modulates the extracellular environment, a polypeptide that modulates checkpoint signaling, a microRNA product that regulates growth, a microRNA product that regulates survival, or a microRNA product that regulates cytolytic capacity; and

b) a second nucleic acid comprising a second promoter, wherein the second nucleic acid is operably linked to a third nucleic acid that encodes a transcriptional activator for the first promoter inducible by drug; and

wherein the system is configured to respond to an amount of the drug that is less than a comparable system utilizing a wild type HEA3 chimeric transcription factor or a wild type HEA4 chimeric transcription factor, or the system has an enhanced transcriptional expression at a given concentration of the drug compared to a system utilizing a wild type HEA3.

42. The system of Claim 41, wherein the transcriptional activator is HEA3 or HEA4.

43. The system of Claim 42, wherein HEA3 is a variant of a wild type HEA3 transcription factor.

44. The system of Claim 42, wherein HEA4 is a variant of a wild type HEA4 transcription factor.

45. The system of Claim 42 or 43, wherein HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, and wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand.

46. The system of Claim 42 or 43, wherein HEA3 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug.

47. The system of Claim 42 or 44, wherein HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the estrogen receptor ligand binding domain comprises at least one mutation that allows selective binding to the drug ligand.

48. The system of Claim 42 or 44, wherein HEA4 comprises an estrogen receptor ligand binding domain (ER-LBD) and a RelA (p65) transactivation domain, wherein the

RelA (p65) transactivation domain comprises at least one mutation that enhances transcriptional activity in response to a drug.

49. The system of any one of Claims 42-48, wherein the variant of the HEA3 or HEA4 chimeric transcription factor comprises p65 phosphomimetic and/or acetylmimetic amino acid substitutions that enhance transcriptional activity in response to the drug ligand.

50. The system of any one of Claims 42, 43, 45, 46 or 49, wherein the variant of a wild type HEA3 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 1-3, 8-11 and/or 121.

51. The system of any one of Claims 42, 43, 45, 46, 49 or 50 wherein the variant of the wild type HEA3 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 12, 13, 14, 19, 20, 21, 22 or 122.

52. The system of any one of Claims 42 or 47-49, wherein the variant of a wild type HEA4 transcription factor comprises an amino acid sequence set forth in SEQ ID Nos: 4-7.

53. The system of any one of Claims 42, 47-49 or 52, wherein the variant of the wild type HEA4 transcription factor is encoded by a nucleic acid sequence set forth in SEQ ID NO: 15, 16, 17 or 18.

54. The system of any one of Claims 2-3, 5, 6, 9-11, 14-40, 42, 43, 45, 46 or 49-51, wherein the transcriptional regulator is a variant of a HEA3 chimeric transcription factor, and wherein the variant comprises amino acid substitutions that allow selective binding to the drug.

55. The system of any one of Claims 41-54, wherein the drug is tamoxifen and/or its metabolites, 4-hydroxytamoxifen, fulvestrant or other estrogen analogs, or CMP8.

56. The system of any one of Claims 41-54, wherein the drug induces a level of expression of the chimeric antigen receptor that is greater than a wild type HEA3 or wild type HEA4 chimeric transcription factor at a concentration of the drug that is at

least 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nM of the drug or at a concentration that is within a range defined by any two of the aforementioned values.

57. The system of any one of Claims 41-56, wherein the drug induces expression of the chimeric antigen receptor at a non-toxic dosing of drug at less than 10 nM drug but not zero.

58. The system of Claim 57, wherein the non-toxic dosing of drug decreases, eliminates or prevents drug side effects in comparison to a dosage for inducing expression with a wild type HEA3 or wild type HEA4 chimeric transcription factor.

59. The system of Claim 58, wherein the side effects are cataracts, constipation, diarrhea, edema, fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vomiting or weight loss.

60. The system of any one of Claims 1-59, wherein the second nucleic acid further comprises:

a polynucleotide encoding a chimeric antigen receptor comprising a ligand binding domain, which is a tumor specific molecule, viral specific molecule, or any other selected molecule expressed on a target cell population, wherein the ligand elicits recognition, modulation, inhibition, and/or elimination by a lymphocyte;
a polynucleotide coding for a polypeptide spacer, wherein the spacer is optionally optimized;
a polynucleotide coding for a transmembrane domain; and
a polynucleotide encoding an intracellular signaling domain.

61. The system of anyone of Claims 41-60, wherein the polypeptide that regulates apoptosis is Survivin.

62. The system of Claim 61, wherein Survivin is encoded by a sequence set forth in SEQ ID NO: 124.

63. The system of Claim 61 or 62, wherein Survivin comprises an amino acid sequence set forth in SEQ ID NO: 123.

64. The system of any one of Claims 1-63, wherein the first promoter is in opposite orientation to the second promoter.

65. The system of any one of Claims 1-64, wherein the ligand binding domain is an antibody fragment, such as a binding fragment.

66. The system of Claim 65, wherein the ligand binding domain is a single chain variable fragment.

67. The system of any one of Claims 1-41 or 63-66, wherein the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, and MAGE A3 TCR or any combination thereof.

68. The system of any one of Claims 1-41 or 63-66, wherein the viral specific molecule is an HIV envelope protein or HIV envelope protein complex, Hepatitis C virus NS3 protein, HbcAg protein, HIV-1 GP120 protein, or Epstein-Barr virus early antigen protein.

69. The system of any one of Claims 65 or 66, wherein the ligand binding domain specifically binds with CD19, CD20, CD22, EGFRvIII, EGFR, EphA2, IL13Ra2, L1CAM, oaGD2, Her2, B7H3, CD33, Mesothelin, ROR-1, FITC and/or VAR2CSA

70. The system of any one of Claims 1-69, wherein the spacer comprises IgG4, IgG4-CH2(L235D, N297Q) or IgG4-CH3.

71. The system of any one of Claims 41-70, wherein the first nucleic acid further comprises a DNA spacer, wherein the spacer is operably linked to the first promoter and operably linked to the first polynucleotide that encodes the chimeric antigen receptor.

72. The system of Claim 71, wherein the DNA spacer is between the first promoter and the first polynucleotide that encodes the chimeric antigen receptor.

73. The system of any one of Claims 71 or 72, wherein the DNA spacer comprises a sequence set forth in SEQ ID NO: 120.

74. The system of any one of Claims 71-73, wherein the DNA spacer comprises a sequence that has 95%, 90%, 85% or 80% sequence identity to SEQ ID NO: 120 or any percent sequence identity in between a range defined by any two aforementioned values.

75. The system of any one of Claims 72-74, wherein the DNA spacer enhances gene expression of the chimeric antigen receptor.

76. The system of any one of Claims 41-75, wherein the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector.

77. The system of Claim 76, wherein both vectors are packaged in a viral vector.

78. The system of Claim 77, wherein the viral vector is an adeno-associated virus or a lentivirus.

79. A chimeric receptor polypeptide coded for by the first nucleic acid of the system of any one of Claims 1-35 or 54-68or the second nucleic acid of the system of any one of Claims 41-78.

80. A host cell, such as a mammalian cell, comprising a system of any one of Claims 1-78.

81. The host cell of Claim 80, wherein the host cell is a precursor T cell.

82. The host cell of Claim 81, wherein the precursor T cell is a hematopoietic stem cell.

83. The host cell of Claim 80, wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells.

84. The host cell according to Claim 80, wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells.

85. A composition comprising a host cell of any one or more of Claims 80-84, in a pharmaceutically acceptable excipient.

86. The composition of Claim 85, comprising a host cell of Claim 81 and a host cell of Claim 82.

87. The composition of Claim 85, comprising a host cell of Claim 81 or 82 and a host cell of Claim 83 or 84.

88. An *in vitro* method for preparing a host cell of any one of Claims 80-84 comprising:

a) providing a system of any one of Claims 1-78; and
b) introducing the system into an isolated T lymphocyte population and expanding each T lymphocyte population *in vitro*.

89. The method of Claim 88, wherein the T lymphocytes are expanded, and wherein the method further comprises culturing the cells in the presence of anti-CD3 and/or anti CD28, and at least one homeostatic cytokine until the cells expand sufficiently for use as a cell infusion.

90. The method of Claim 88 or 89, wherein the isolated T lymphocyte population comprises precursor T cells.

91. The method of Claim 90, wherein the precursor T cells are hematopoietic stem cells.

92. The method of any one of Claims 88-91, wherein the lymphocyte is CD8+ or CD4+.

93. A method of treating, inhibiting, or ameliorating a disease in a subject in need thereof comprising:

administering to the subject the host cell, preferably a mammalian host cell, of any one of Claims 80-84 or at least one composition or product combination of any one or more of Claims 85-87.

94. The method of Claim 93, wherein the disease is cancer or a viral disease.

95. The method of Claim 93 or 94, wherein the subject is identified or selected to receive an anti-cancer therapy.

96. The method of any one of Claims 93-95, wherein the subject is identified or selected to receive an anti-viral therapy.

97. The method of any one of Claims 93-96, further comprising measuring or evaluating an inhibition of the disease.

98. The method of any one of Claims 93-97, further comprising providing said subject an additional anti-cancer therapy or anti-viral therapy before, during, or after administration of the cells of any one or more of Claims 80-84 or at least one composition or product combination of any one or more of Claims 85-87.

99. The method of any one or more of Claims 93-98, wherein the cells of any one or more of Claims 80-84 or at least one composition or product combination of any one or more of Claims 85-87 are administered to said subject by adoptive cell transfer.

100. The method of any one or more of Claims 93-99, wherein the host cells of any one or more of Claims 80-84 or at least one composition or product combination of any one or more of Claims 85-87 are administered to said subject after said subject has received another form of anti-cancer therapy or anti-viral therapy.

101. The method of any one or more of Claims 93-100, further comprising administering a drug that induces expression of a transgene in the host cell, such as a mammalian cell, or composition for the treatment of cancer or a viral infection.

102. The method of Claim 101, wherein the drug is tamoxifen and/or its metabolites, fulvestrant and/or other estrogen analogs or CMP8.

103. The method of Claim 102, wherein tamoxifen is administered at a dose range of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg/dose or within a range defined by any two of the aforementioned values.

104. The method of Claim 102, wherein the fulvestrant is administered at a dose range of 250, 300, 350, 400, 450 or 500 mg/dose mg/dose or within a range defined by any two of the aforementioned values.

105. The method of Claim 102, wherein the CMP8 is administered at a dose range to provide 30, 40 or 50 nM of drug levels in serum, or within a range defined by any two of the aforementioned values.

106. The method of any one of Claims 94-105, wherein the cancer is a solid tumor or hematologic malignancy.

107. The method of 106, wherein the solid tumor is selected from the group consisting of a breast cancer, brain cancer, lung cancer, colon cancer, renal cancer, pancreatic cancer, prostate cancer, and ovarian cancer.

108. A use of the host cell of any one of or more of Claims 80-84 or at least one composition or product combination of any one or more of Claims 85-88 in combination with a drug that induces expression of a transgene in the host cell or composition for the treatment of cancer or a viral infection.

109. The use of Claim 108, wherein the drug is tamoxifen and/or its metabolites, fulvestrant and/or other estrogen analogs or CMP8.

110. The use of Claim 109, wherein tamoxifen is administered at a dose range of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg/dose or within a range defined by any two of the aforementioned values.

111. The use of Claim 109, wherein the fulvestrant is administered at a dose range of 250, 300, 350, 400, 450 or 500 mg/dose or within a range defined by any two of the aforementioned values.

112. The use of claim 109, wherein the CMP8 is administered at a dose range to provide 30, 40 or 50 nM of drug levels in serum, or within a range defined by any two of the aforementioned values.

113. The use of any one of Claims 108-112, wherein the cancer is a solid tumor or hematologic malignancy.

114. The use of Claim 113, wherein the solid tumor is selected from the group consisting of a breast cancer, brain cancer, lung cancer, colon cancer, renal cancer, pancreatic cancer, prostate cancer, and ovarian cancer.

115. A method of performing cellular immunotherapy in a subject having cancer or a viral infection comprising: administering the host cells of any one or more of Claims 80-84 or at least one composition or product combination of any one or more of Claims 85-87 to the subject and administering a drug that induces expression of a transgene in the composition or the host cells.

116. The method of Claim 115, wherein the cancer is selected from a solid tumor or hematologic malignancy.

117. The method of Claim 116, wherein the solid tumor is selected from the group consisting of a breast cancer, brain cancer, lung cancer, colon cancer, renal cancer, pancreatic cancer, prostate cancer, and ovarian cancer.

118. Use of the host cell of any one of or more of Claims 80-84 or at least one composition or product combination of any one or more of Claims 85-87 as a medicament.

FIG 1A

FIG 1B

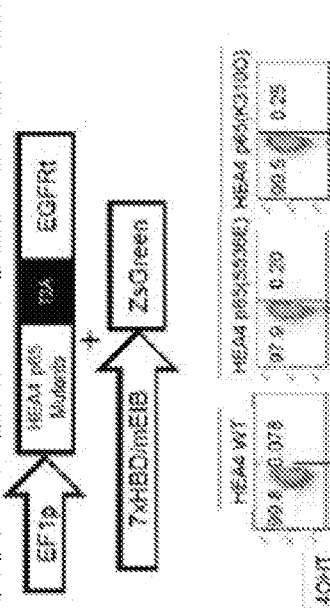


FIG 1C

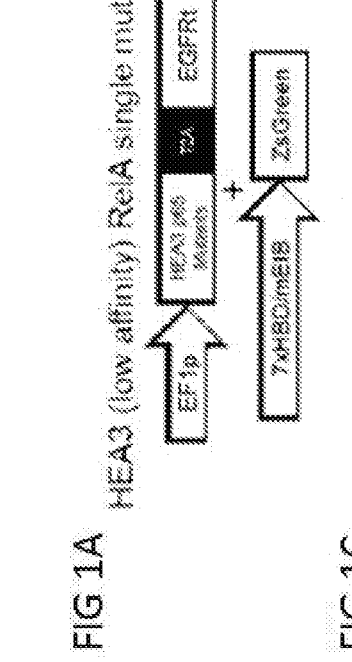
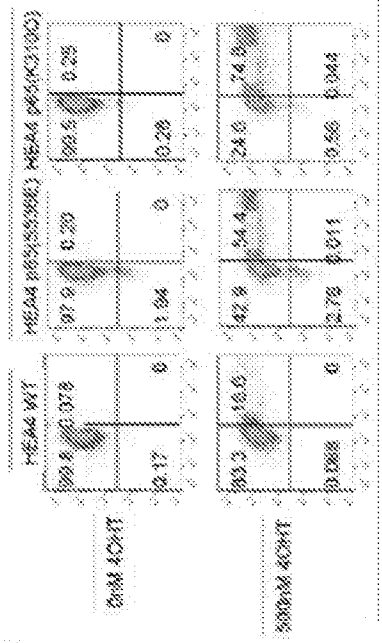


FIG 1D



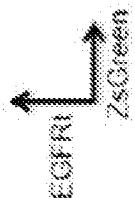


FIG 1E

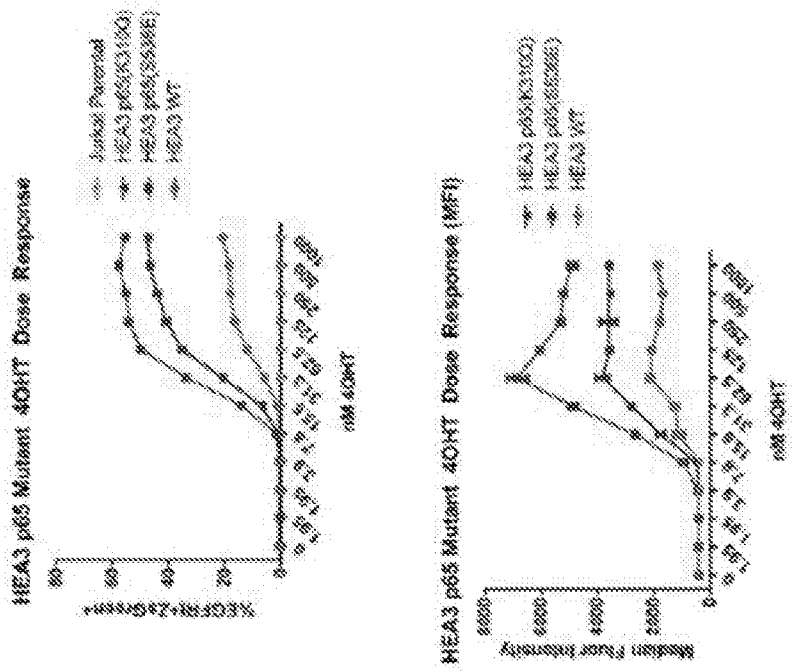

HEA3 p65 Mutant 4OHT Dose Response
%ECFP+ZsG+
nM 4OHT
HEA3 p65 Mutant 4OHT Dose Response (MFI)
Median Fluor Intensity
nM 4OHT
Jurkat Parental
HEA3 p65(K310Q)
HEA3 p65(S536E)
HEA3 WT

FIG 1F

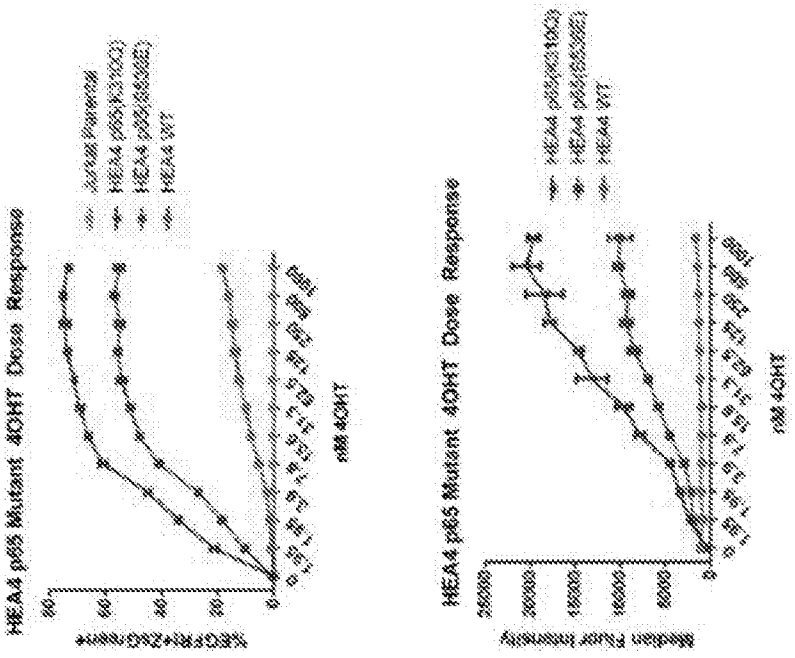

HEA4 p65 Mutant 4OHT Dose Response
%ECFP+ZsG+
nM 4OHT
HEA4 p65 Mutant 4OHT Dose Response
Median Fluor Intensity
nM 4OHT
Jurkat Parental
HEA4 p65(K310Q)
HEA4 p65(S536E)
HEA4 WT

FIG 2A

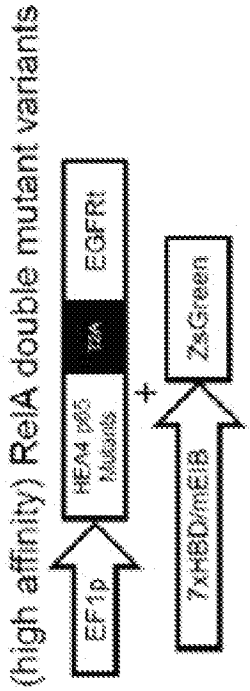

HEA4 (high affinity) RelA double mutant variants
EF1p
HEA4 (M3 Mutants)
T2A
EGFRt
7xHBDmE1B
ZsGreen

FIG 2B

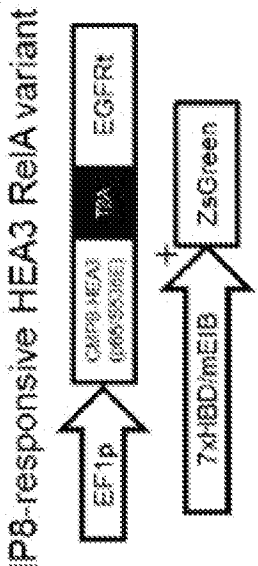
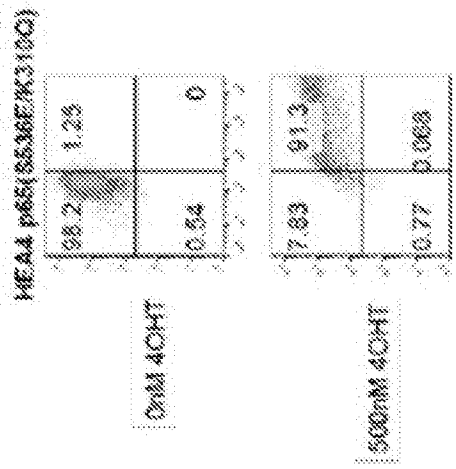

CMP8-responsive HEA3 RelA variant
EF1p
CMP8-HEA3 (M3 Mutants)
T2A
EGFRt
7xHBDmE1B
ZsGreen

FIG 2C


HEA4 pRS(63Mb)EW(310D)
98.2
1.25
0.54
0
7.83
91.3
0.77
0.068
0nM 4OHT
500nM 4OHT

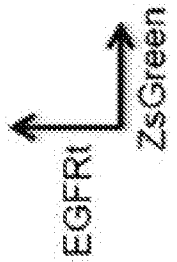

EGFRt
ZsGreen

FIG 2D

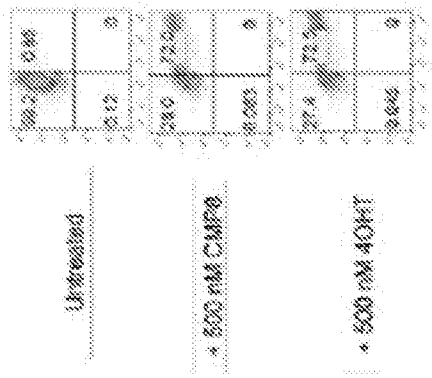
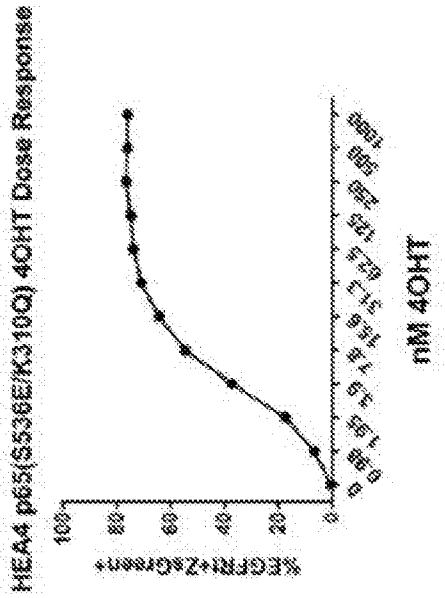

Untreated
+ 500 nM OHT

FIG 2E


HEA4 p65(S536E/K310Q) 4OHT Dose Response
%EGFRI+ZsGreen+
nM 4OHT

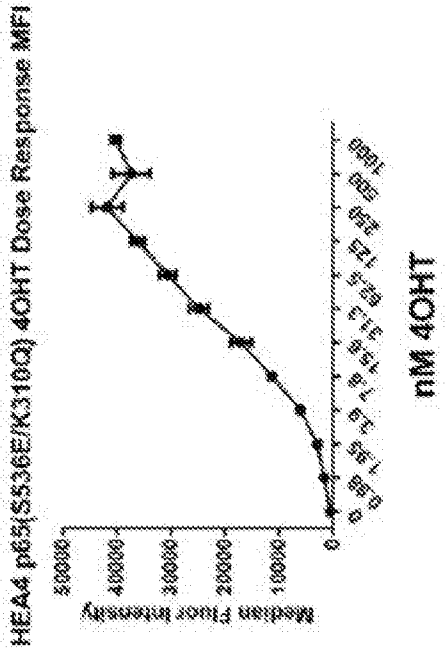
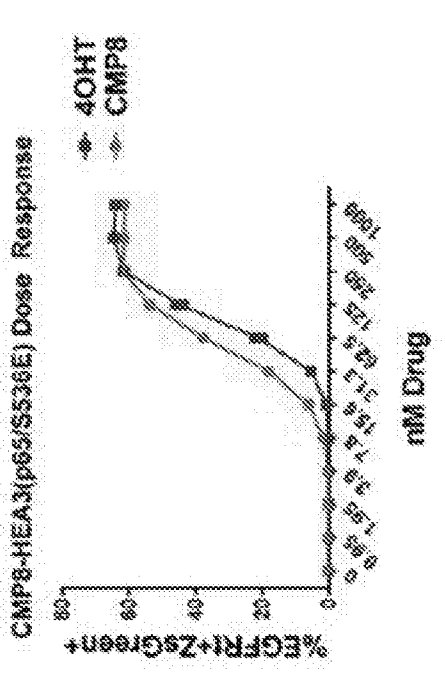
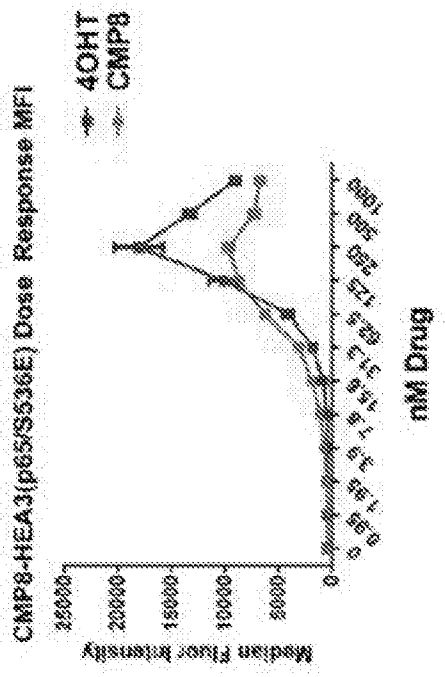

HEA4 p65(S536E/K310Q) 4OHT Dose Response MFI
Median Fluor Intensity
nM 4OHT

FIG 2F


CMP8-HEA3(p65/S536E) Dose Response
4OHT
CMP8
%EGFRI+ZsGreen+
nM Drug


CMP8-HEA3(p65/S536E) Dose Response MFI
4OHT
CMP8
Median Fluor Intensity
nM Drug

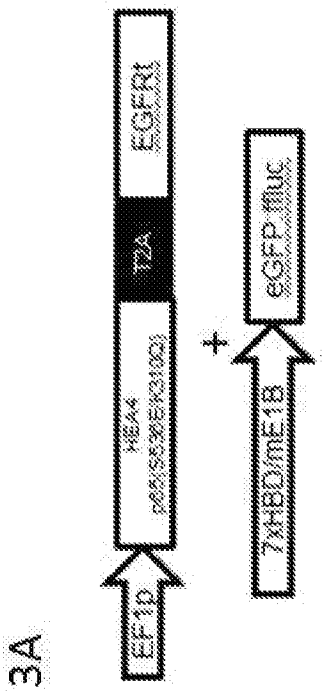


FIG 3A

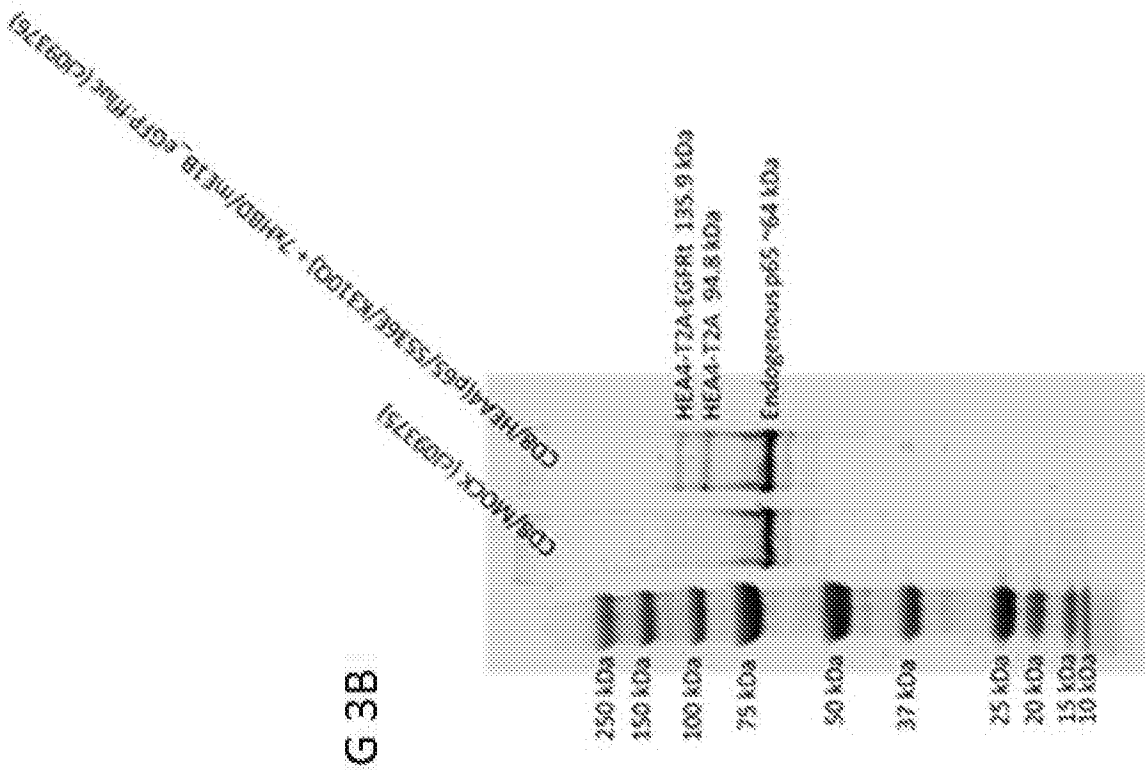

Cetuximab (IgG1)
Cetuximab-Fab-pHLEP-ZsGreen1 + Trastuzumab-Fab-pHLEP-ZsGreen1 (IgG1)
HER4-T2A-EGFR 135.9 kDa
HER4-T2A 94.8 kDa
Endogenous p65 ~64 kDa
250 kDa
150 kDa
100 kDa
75 kDa
50 kDa
37 kDa
25 kDa
20 kDa
15 kDa
10 kDa

FIG 3B

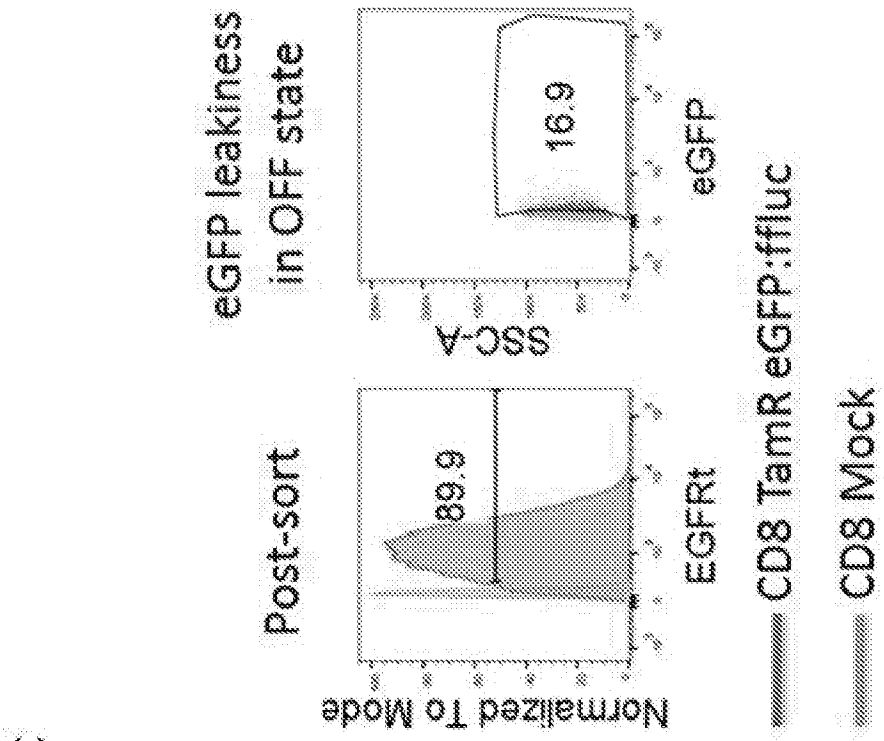

eGFP leakiness
in OFF state
Post-sort
89.9
16.9
SSC-A
EGFRt
eGFP
Normalized To Mode
CD8 TamR eGFP:ffluc
CD8 Mock

FIG 3C

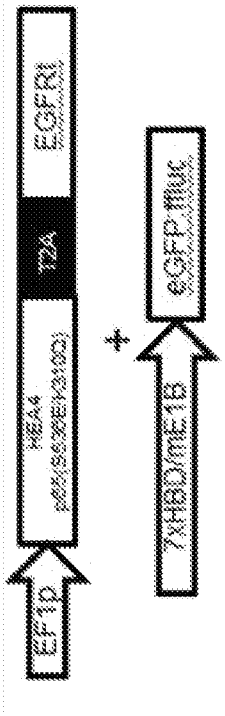


FIG 4A

FIG 4B

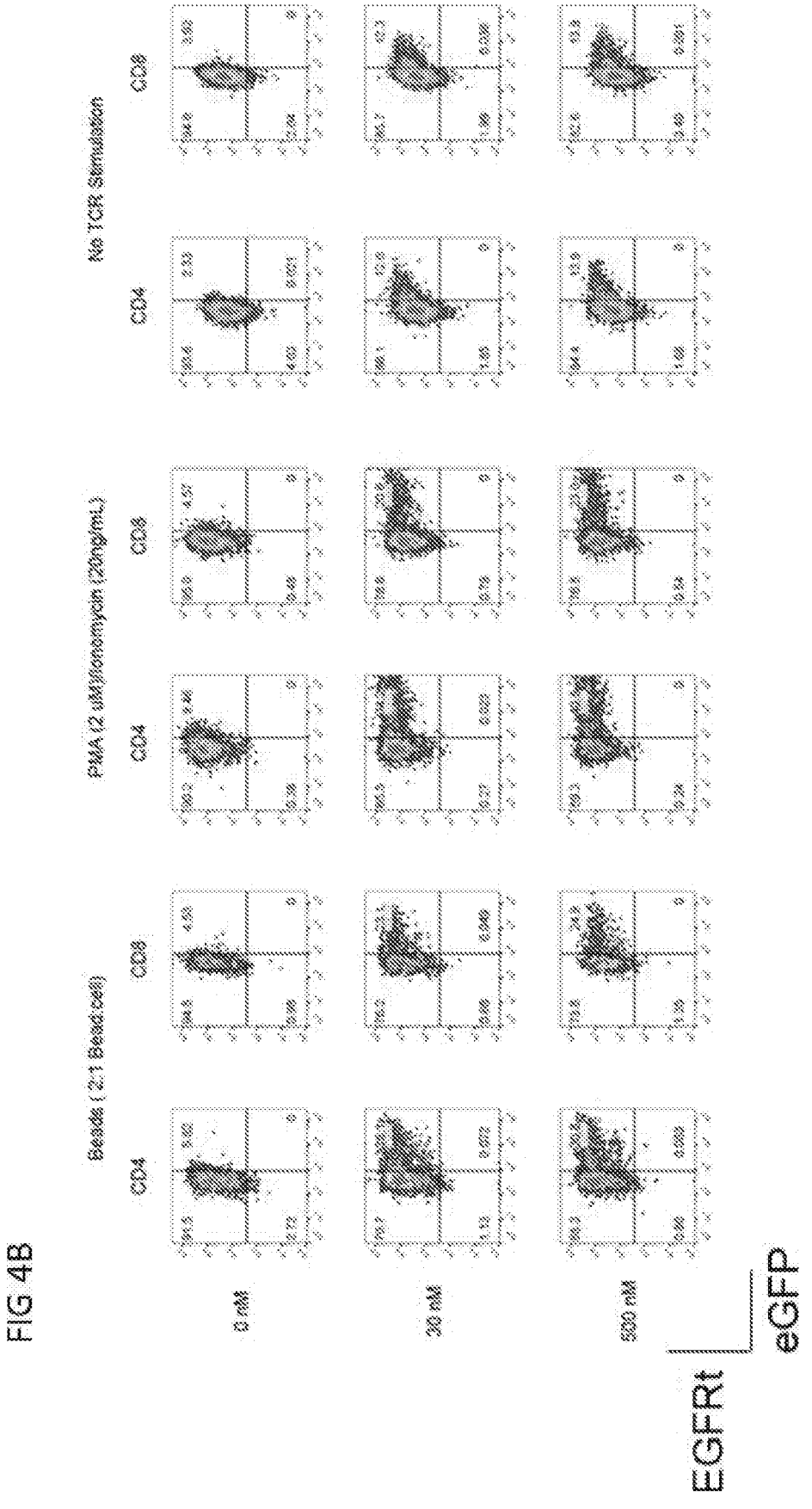

No TCR Stimulation
PMA (2 uM)/Ionomycin (20ng/mL)
Beads (2:1 Bead:cell)
CD4
CD8
0 nM
30 nM
500 nM
EGFRt
eGFP

FIG 5A

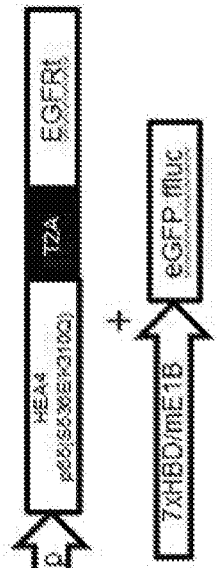


FIG 5B

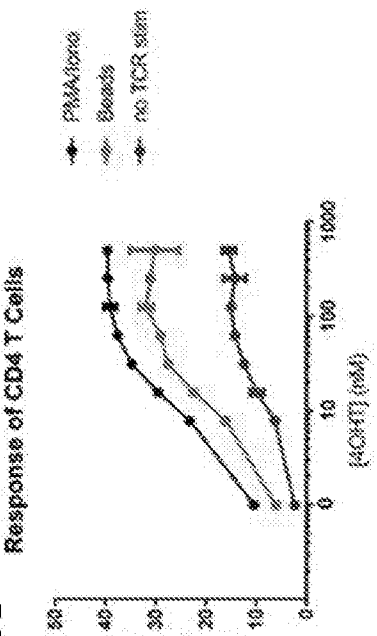


FIG 5C

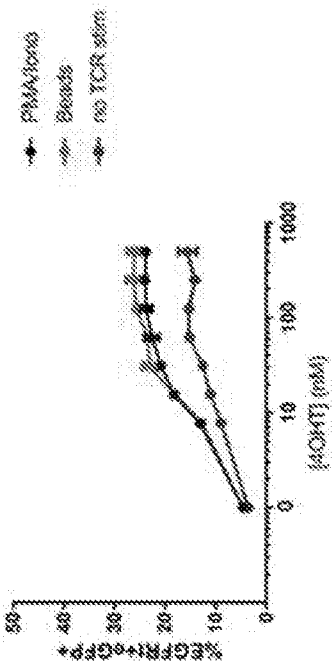


FIG 5D

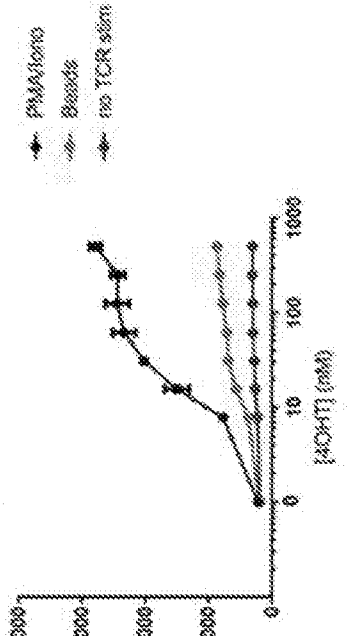
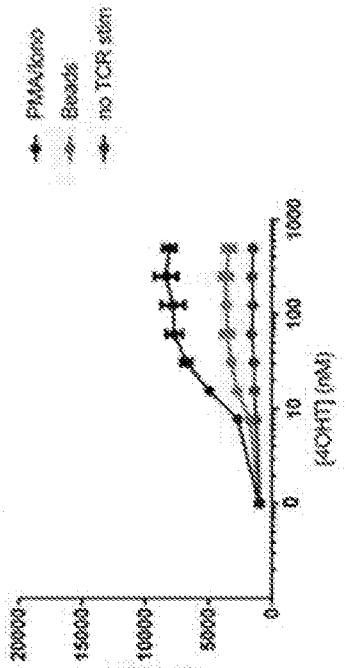


FIG 5E



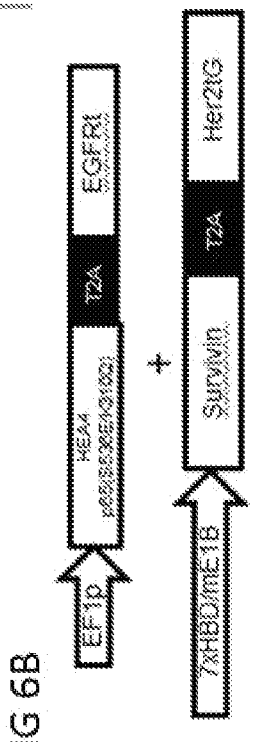


FIG 6A

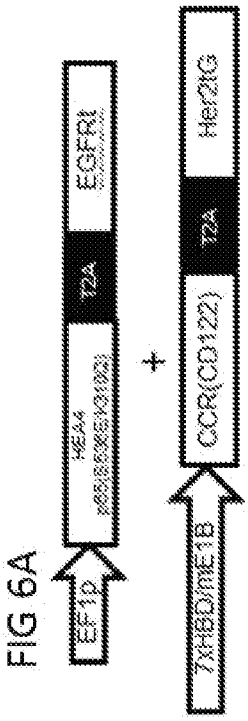


FIG 6B

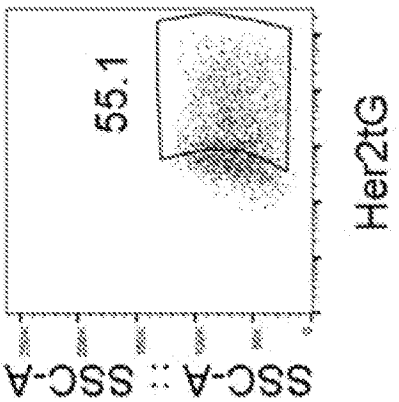


FIG 6C

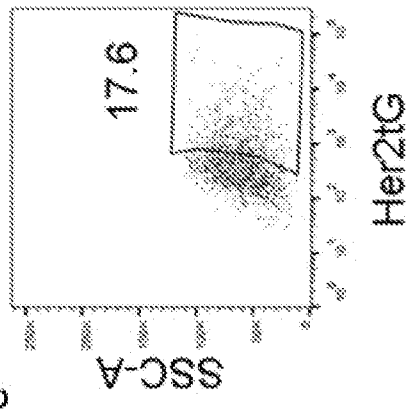


FIG 6D

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/65597

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 35/12, A61K 35/28, A61K 38/17 (2018.01)
CPC - A61K 2039/5156, A61K 2039/5158, C07K 16/2896, A61K 39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/157432 A1 (SEATTLE CHILDREN'S HOSPITAL (DBA SEATTLE CHILDREN'S RESEARCH INSTITUTE) 15 October 2015 (15.10.2015) para [0007]-[0013]; [0059]; [0083]-[0087]; [0144]-[0146]; Tables 10 and 11.	1-7, 41-48
A	US 2003/0143559 A1 (BRACKEN et al.) 31 July 2003 (31.07.2003) para [0021]-[0043].	1, 41

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 February 2018	06 MAR 2018

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/65597

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8-40, 49-118
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.