

bind significantly to the second portion of the first ligand. Examples of first ligand binding units include, but are not limited to, FKBP12 multimerizing regions, or variants, such as FKBP12v36, examples of second ligand binding units are, for example, FRB or FRB variant multimerizing regions. Examples of a third ligand binding unit include, for example, but are not limited to,

5 FKBP12 multimerizing regions, or variants, such as FKBP12v36. In certain embodiments, the first ligand binding unit is FKBP12, and the third ligand binding unit is FKBP12v36. In certain embodiments, the first ligand is rapamycin, or a rapalog, and the second ligand is rimiducid (AP1903).

10 The multimerizing regions, such as FKBP12/FRB, FRB/FKBP12, and FKBP12v36, may be located amino terminal to the pro-apoptotic polypeptide or costimulatory polypeptide, or, in other examples, may be located carboxyl terminal to the pro-apoptotic polypeptide or costimulatory polypeptide. Additional polypeptides, such as, for example, linker polypeptides, stem polypeptides, spacer polypeptides, or in some examples, marker polypeptides, may be located between the

15 multimerizing region and the pro-apoptotic polypeptide or costimulatory polypeptide, in the chimeric polypeptides.

Thus, provided in some embodiments are modified cells, comprising a first polynucleotide encoding a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide

20 comprises (i) a pro-apoptotic polypeptide region; (ii) a FKBP12-Rapamycin-Binding (FRB) domain polypeptide, or FRB variant polypeptide region; and (iii) a FKBP12 or FKBP12 variant polypeptide region (FKBP12v); and a second polynucleotide encoding a chimeric costimulating polypeptide, wherein the chimeric costimulating polypeptide comprises one or more, for example, 1, 2, or 3 FKBP12 variant polypeptide regions and i) a MyD88 polypeptide region or a truncated MyD88

25 polypeptide region lacking the TIR domain; or ii) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain, and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain. In a **first** aspect, there is provided a modified cell, comprising a) a first polynucleotide encoding a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises (i) a pro-apoptotic polypeptide region; (ii) a

30 FKBP12-Rapamycin-Binding (FRB) polypeptide region, or FRB variant polypeptide region; and (iii) a FKBP12 polypeptide region; and b) a second polynucleotide encoding a chimeric costimulating polypeptide, wherein the chimeric costimulating polypeptide comprises two FKBP12 variant polypeptide regions and i) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain; or ii) a MyD88 polypeptide region or a truncated MyD88

35 polypeptide region lacking the TIR domain, and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain. In some embodiments, the modified cell further comprises a third polynucleotide encoding a chimeric antigen receptor or a recombinant T cell receptor.

Also provided in some embodiments is a nucleic acid comprising a promoter operably linked to

40 a first polynucleotide encoding a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises (i) a pro-apoptotic polypeptide region; (ii) a FKBP12-Rapamycin-Binding (FRB) domain polypeptide, or FRB variant polypeptide region; and (iii) a FKBP12 or FKBP12 variant polypeptide region (FKBP12v); and a second polynucleotide encoding a chimeric

costimulating polypeptide, wherein the chimeric costimulating polypeptide comprises one or more, for example, 1, 2, or 3 FKBP12 variant polypeptide regions and i) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain; or ii) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain, and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain. In a **second** aspect, there is provided a nucleic acid comprising a promoter operably linked to a) a first polynucleotide encoding a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises (i) a pro-apoptotic polypeptide region; (ii) a FKBP12-Rapamycin-Binding (FRB) polypeptide region, or FRB variant polypeptide region; and (iii) a FKBP12 polypeptide region; and b) a second polynucleotide encoding a chimeric costimulating polypeptide, wherein the chimeric costimulating polypeptide comprises two FKBP12 variant polypeptide regions and i) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain; or ii) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain, and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain. In some embodiments, the chimeric costimulating polypeptide comprises a truncated MyD88 polypeptide region lacking the TIR domain and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain. In some embodiments, the promoter is operably linked to a third polynucleotide, wherein the third polynucleotide encodes a chimeric antigen receptor or a recombinant T cell receptor. In some embodiments, the pro-apoptotic polypeptide is a Caspase-9 polypeptide, wherein the Caspase-9 polypeptide lacks the CARD domain. In some embodiments, the cell is a T cell, tumor infiltrating lymphocyte, NK-T cell, or NK cell. In a **third** aspect, there is provided a modified cell, comprising the nucleic acid of the second aspect.

Also provided in some embodiments are kits or compositions comprising nucleic acid comprising a first polynucleotide encoding a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises (i) a pro-apoptotic polypeptide region; (ii) a FKBP12-Rapamycin-Binding (FRB) domain polypeptide region, or variant thereof; and (iii) a FKBP12 polypeptide or FKBP12 variant polypeptide region (FKBP12v); and a second polynucleotide encoding a chimeric costimulating polypeptide, wherein the chimeric costimulating polypeptide comprises one or more, for example, 1, 2, or 3 FKBP12 variant polypeptide regions and i) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain; or ii) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain, and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain.

In some embodiments, methods are provided for expressing a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises a pro-apoptotic polypeptide region; a FRB polypeptide or FRB variant polypeptide region; and a FKBP12 polypeptide region of the present embodiments, comprising contacting a nucleic acid of the present embodiments with a cell under conditions in which the nucleic acid is incorporated into the cell, whereby the cell expresses the chimeric pro-apoptotic polypeptide from the incorporated nucleic acid.

In some embodiments, methods are provided for stimulating an immune response in a subject, comprising: transplanting modified cells of the present embodiments into the subject, and after (a), administering an effective amount of a ligand that binds to the FKBP12 variant polypeptide region of the chimeric costimulating polypeptide to stimulate a cell mediated immune response. In some embodiments, methods are provided for administering a ligand to a subject who has undergone cell therapy using modified cells, comprising administering a ligand that binds to the FKBP variant

region of the chimeric costimulating polypeptide to the human subject, wherein the modified cells comprise modified cells of the present embodiments the present embodiments. Also provided are methods for treating a subject having a disease or condition associated with an elevated expression of a target antigen expressed by a target cell, comprising a) transplanting an effective amount of modified cells into the subject; wherein the modified cells comprise a modified cell of the present embodiments, wherein the modified cell comprises a chimeric antigen receptor or a recombinant T cell receptor comprising an antigen recognition moiety that binds to the target antigen, and b) after a), administering an effective amount of a ligand that binds to the FKBP12 variant polypeptide region of the chimeric costimulating polypeptide to reduce the number or concentration of target antigen or target cells in the subject. Also provided are methods for reducing the size of a tumor in a subject, comprising a) administering a modified cell of the present embodiments to the subject, wherein the cell comprises a chimeric antigen receptor or a recombinant T cell receptor comprising an antigen recognition moiety that binds to an antigen on the tumor; and b) after a), administering an effective amount of a ligand that binds to the FKBP12 variant polypeptide region of the chimeric costimulating polypeptide to reduce the size of the tumor in the subject. Also provided are methods for controlling survival of transplanted modified cells in a subject, comprising transplanting modified cells of the present embodiments into the subject; and administering to the subject rapamycin or a rapalog that binds to the FRB polypeptide or FRB variant polypeptide region of the chimeric pro-apoptotic polypeptide in an amount effective to kill at least 30% of the modified cells that express the chimeric pro-apoptotic polypeptide.

In a **fourth** aspect, there is provided use of any of the modified cells of the first or third aspects in the manufacture of a medicament for stimulating an immune response in a subject, wherein:

- a) the modified cells are to be transplanted into the subject, and
- b) after (a), an effective amount of a ligand that binds to the FKBP12 variant polypeptide region of the chimeric costimulating polypeptide is to be administered to stimulate a cell mediated immune response.

In a **fifth** aspect, there is provided use of a ligand that binds to the FKBP12 variant region of the chimeric costimulating polypeptide in the manufacture of a medicament for administering a ligand to a subject who has undergone cell therapy using modified cells, wherein the modified cells comprise any of the modified cells of the first or third aspects.

In a **sixth** aspect, there is provided use of any of the modified cells of the first or third aspects in the manufacture of a medicament for treating a subject having a disease or condition associated with an elevated expression of a target antigen expressed by a target cell, wherein:

- a) an effective amount of the modified cells is to be transplanted into the subject; wherein the modified cell comprises a chimeric antigen receptor or a recombinant T cell receptor comprising an antigen recognition moiety that binds to the target antigen, and
- b) after a), an effective amount of a ligand that binds to the FKBP12 variant polypeptide region of the chimeric costimulating polypeptide is to be administered to reduce the number or concentration of target antigen or target cells in the subject.

In a **seventh** aspect, there is provided use of any of the modified cells of the first or third aspects in the manufacture of a medicament for reducing the size of a tumor in a subject, wherein:

a) the modified cell of the first or third aspects is to be administered to the subject, wherein the cell comprises a chimeric antigen receptor or a recombinant T cell receptor comprising an antigen recognition moiety that binds to an antigen on the tumor; and

b) after a), an effective amount of a ligand that binds to the FKBP12 variant polypeptide region of the chimeric costimulating polypeptide is to be administered to reduce the size of the tumor in the subject.

In an **eighth** aspect, there is provided use of rapamycin or a rapalog that binds to the FRB polypeptide or FRB variant polypeptide region of the chimeric pro-apoptotic polypeptide in the manufacture of a medicament for controlling survival of transplanted modified cells in a subject, wherein:

a) any of the modified cells of the first or third aspects are to be transplanted into the subject; and

b) after a), the rapamycin or rapalog is to be administered in an amount effective to kill at least 30% of the modified cells that express the chimeric pro-apoptotic polypeptide.

In other embodiments, modified cells are provided comprising a first polynucleotide encoding a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises i) a pro-apoptotic polypeptide region; and ii) a FKBP12 variant polypeptide region; and a second polynucleotide encoding a chimeric costimulating polypeptide, wherein the chimeric costimulating polypeptide comprises a FKBP12-Rapamycin Binding (FRB) domain polypeptide or FRB variant polypeptide region; a FKBP12 polypeptide or FKBP12 variant polypeptide region; and a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain, or a MyD88 polypeptide region, or a truncated MyD88 polypeptide region lacking the TIR domain and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain. In a **ninth** aspect, there is provided a modified cell comprising a) a first polynucleotide encoding a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises i) a pro-apoptotic polypeptide region; and ii) a FKBP12 variant polypeptide region; and b) a second polynucleotide encoding a chimeric costimulating polypeptide, wherein the chimeric costimulating polypeptide comprises i) a FKBP12-Rapamycin Binding (FRB) polypeptide region or FRB variant polypeptide region; ii) a FKBP12 polypeptide region; and iii) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain, or a MyD88 polypeptide region, or a truncated MyD88 polypeptide region lacking the TIR domain and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain.

In some embodiments, the chimeric costimulating polypeptide comprises a truncated MyD88 polypeptide region lacking the TIR domain and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain. In some embodiments, the cell further comprises a third polynucleotide, wherein the third polynucleotide encodes a chimeric antigen receptor or a recombinant T cell receptor.

In some embodiments, nucleic acids are provided, wherein the nucleic acids comprise a promoter operably linked to a first polynucleotide encoding a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises i) a pro-apoptotic polypeptide region; and i) a FKBP12 variant polypeptide region; and a second polynucleotide encoding a chimeric

5 costimulating polypeptide, wherein the chimeric costimulating polypeptide comprises i) a FKBP12-Rapamycin Binding (FRB) domain polypeptide or FRB variant polypeptide region; ii) a FKBP12 polypeptide region; and ii) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain, or a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular

10 domain. In a **tenth** aspect, there is provided a nucleic acid comprising a promoter operably linked to a) a first polynucleotide encoding a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises i) a pro-apoptotic polypeptide region; and ii) a FKBP12 variant polypeptide region; and b) a second polynucleotide encoding a chimeric costimulating polypeptide, wherein the chimeric costimulating polypeptide comprises i) a FKBP12-Rapamycin

15 Binding (FRB) polypeptide region or FRB variant polypeptide region; ii) a FKBP12 polypeptide region; and iii) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain, or a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain.

In some embodiments, the chimeric costimulating polypeptide comprises a truncated MyD88

20 polypeptide region lacking the TIR domain and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain. In some embodiments, the promoter is operably linked to a third polynucleotide, wherein the third polynucleotide encodes chimeric antigen receptor or a recombinant T cell receptor. In some embodiments, the pro-apoptotic polypeptide is a Caspase-9 polypeptide, wherein the Caspase-9 polypeptide lacks the CARD domain. In some embodiments,

25 the cell is a T cell, tumor infiltrating lymphocyte, NK-T cell, or NK cell. Also provided are kits or compositions comprising nucleic acids comprising polynucleotides of the present embodiments. Also provided are methods for expressing a chimeric pro-apoptotic polypeptide and a chimeric costimulating polypeptide, wherein a) the chimeric pro-apoptotic polypeptide comprises i) a pro-apoptotic polypeptide region; and ii) a FKBP12 variant polypeptide region; and b) the chimeric

30 costimulating polypeptide comprises a FRB or FRB variant polypeptide region; a FKBP12 polypeptide region; and a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain, or a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain comprising contacting a nucleic acid is a nucleic acid comprising a promoter operably

35 linked to a polynucleotide coding for a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises a) a pro-apoptotic polypeptide region; b) a FKBP12-Rapamycin binding domain (FRB) polypeptide or FRB variant polypeptide region; and c) a FKBP12 variant polypeptide region, with a cell under conditions in which the nucleic acid is incorporated into the cell, whereby the cell expresses the chimeric pro-apoptotic polypeptide and

40 the chimeric costimulating polypeptide from the incorporated nucleic acid.

In an **eleventh** aspect, there is provided a modified cell comprising a nucleic acid of the tenth aspect.

In a **twelfth** aspect, there is provided use of any of the modified cells of the ninth or eleventh aspects in the manufacture of a medicament for stimulating an immune response in a subject, wherein:

a) the modified cells are to be transplanted into the subject, and

b) after (a), an effective amount of a rapamycin or a rapalog that binds to the FRB polypeptide or FRB variant polypeptide region of the chimeric stimulating polypeptide is to be administered to stimulate a cell mediated immune response.

In a **thirteenth** aspect, there is provided use of rapamycin or a rapalog in the manufacture of a medicament for administering a ligand to a subject who has undergone cell therapy using modified cells, wherein the modified cells comprise any of the modified cells of the ninth or eleventh aspects.

In a **fourteenth** aspect, there is provided use of any of the modified cells of the ninth or eleventh aspects in the manufacture of a medicament for treating a subject having a disease or condition associated with an elevated expression of a target antigen expressed by a target cell, wherein:

a) an effective amount of modified cells is to be transplanted into the subject; wherein the modified cell comprises a chimeric antigen receptor or a recombinant T cell receptor comprising an antigen recognition moiety that binds to the target antigen, and

b) after a), an effective amount of rapamycin or a rapalog that binds to the FRB polypeptide or FRB variant region of the chimeric stimulating polypeptide is to be administered to reduce the number or concentration of target antigen or target cells in the subject.

In a **fifteenth** aspect, there is provided use of any of the modified cells of the ninth or eleventh aspects in the manufacture of a medicament for reducing the size of a tumor in a subject, wherein:

a) the modified cell of the ninth or eleventh aspect is to be administered to the subject, wherein the cell comprises a chimeric antigen receptor or a recombinant T cell receptor comprising an antigen recognition moiety that binds to an antigen on the tumor; and

b) after a), an effective amount of rapamycin or a rapalog that binds to the FRB or FRB variant polypeptide region of the chimeric stimulating polypeptide is to be administered to reduce the size of the tumor in the subject.

In a **sixteenth** aspect, there is provided use of a ligand that binds to the FKBP12 variant polypeptide region of the chimeric pro-apoptotic polypeptide in the manufacture of a medicament for controlling survival of transplanted modified cells in a subject, wherein:

a) any of the modified cells of the ninth or eleventh aspects are to be transplanted into the subject, and

b) after (a), the ligand is to be administered in an amount effective to kill at least 90% of the modified cells that express the chimeric pro-apoptotic polypeptide.

Also provided in the present application is a nucleic acid comprising a promoter operably linked to a polynucleotide coding for a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises a) a pro-apoptotic polypeptide region; b) a FKBP12-Rapamycin binding domain (FRB) polypeptide or FRB variant polypeptide region; and c) a FKBP12 variant polypeptide region. In a **seventeenth** aspect, there is provided a nucleic acid comprising a promoter operably linked to a polynucleotide coding for a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises a) a pro-apoptotic polypeptide region; b) a FKBP12-Rapamycin binding (FRB) polypeptide region or FRB variant polypeptide region; and c) a FKBP12 variant polypeptide region. In some embodiments, wherein the FKBP12 variant comprises an amino acid substitution at amino acid residue 36. In some embodiments, the FKBP12 variant polypeptide region is a FKBP12v36 polypeptide region. In some embodiments, the FRB variant polypeptide region is selected from the group consisting of KLV (T2098L) (FRBL), KTF (W2101F), and KLF (T2098L, W2101F). In some embodiments, a chimeric pro-apoptotic polypeptide encoded by a nucleic acid of the present embodiments is provided. In some embodiments, modified cells are provided that are transfected or transduced with a nucleic acid of the present embodiments. In some embodiments, the modified cells comprise a polynucleotide that encodes a chimeric antigen receptor or a recombinant TCR. In some embodiments, methods are provided of controlling survival of transplanted modified cells in a subject, comprising: a) transplanting modified cells of the present embodiments, wherein the modified cells comprise a nucleic acid comprising a promoter operably linked to a polynucleotide coding for a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises a) a pro-apoptotic polypeptide region; b) a FKBP12-Rapamycin binding domain (FRB) polypeptide or FRB variant polypeptide region; and c) a FKBP12 variant polypeptide region. of the present embodiments into the subject; and b) after (a), administering to the subject i) a first ligand that binds to the FRB or FRB variant polypeptide region of the chimeric pro-apoptotic polypeptide; or ii) a second ligand that binds to the FKBP12 variant polypeptide region of the chimeric pro-apoptotic polypeptide wherein the first ligand or the second ligand are administered in an amount effective to kill at least 30% of the modified cells that express the chimeric pro-apoptotic polypeptide.

Autologous T cells expressing chimeric antigen receptors (CARs) directed toward tumor-associated antigens (TAAs) have had a transformational effect in initial clinical trials on the treatment of certain types of leukemias ("liquid tumors") and lymphomas with objective response (OR) rates approaching 90%. Despite their great clinical promise and the predictable accompanying enthusiasm, this success is tempered by the observed high level of on-target, off-tumor adverse events, typical of a cytokine release syndrome (CRS). To maintain the benefit of these revolutionary treatments while minimizing the risk, a tunable safety switch has been developed, in order to control the activity level of CAR-expressing T cells. An inducible costimulatory chimeric polypeptide allows for a sustained, modulated control of a chimeric antigen

for example, the AP1903-binding polypeptide FKBP12v36, by administering rimiducid (AP1903). In some examples, the Caspase-9 polypeptide includes amino acid substitutions that result in a lower level of basal apoptotic activity as part of the inducible chimeric polypeptide, than the wild type Caspase-9 polypeptide.

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In some embodiments, the nucleic acid encoding the chimeric polypeptides of the present application further comprise a polynucleotide encoding a chimeric antigen receptor, a T cell receptor, or a T cell receptor-based chimeric antigen receptor. In some embodiments, the chimeric antigen receptor comprises (i) a transmembrane region, (ii) a T cell activation molecule, and (iii) an antigen recognition moiety. Also provided are modified cells transfected or transduced with a nucleic acid discussed herein

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In some embodiments of the present application, the cells are transduced or transfected with a viral vector. The viral vector may be, for example, but not limited to, a retroviral vector, such as, for example, but not limited to, a murine leukemia virus vector; an SFG vector; and adenoviral vector, or a lentiviral vector.

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In some embodiments, the cell is isolated. In some embodiments, the cell is in a human subject. In some embodiments, the cell is transplanted in a human subject.

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In some embodiments, personalized treatment is provided wherein the stage or level of the disease or condition is determined before administration of the multimeric ligand, before the administration of an additional dose of the multimeric ligand, or in determining method and dosage involved in the administration of the multimeric ligand. These methods may be used in any of the methods of any of the diseases or conditions of the present application. Where these methods of assessing the patient before administering the ligand are discussed in the context of graft versus host disease, it is understood that these methods may be similarly applied to the treatment of other conditions and diseases. Thus, for example, in some embodiments of the present application, the method comprises administering therapeutic cells to a patient, and further comprises identifying a presence or absence of a condition in the patient that requires the removal of transfected or transduced therapeutic cells from the patient; and administering a multimeric ligand that binds to the multimerizing region, maintaining a subsequent dosage of the multimeric ligand, or adjusting a subsequent dosage of the multimeric ligand to the patient based on the presence or absence of the condition identified in the patient. And, for example, in other embodiments of the present

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What is claimed is:

1. A modified cell, comprising
 - a) a first polynucleotide encoding a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises
 - (i) a pro-apoptotic polypeptide region;
 - (ii) a FKBP12-Rapamycin-Binding (FRB) polypeptide region, or FRB variant polypeptide region; and
 - (iii) a FKBP12 polypeptide region; and
 - b) a second polynucleotide encoding a chimeric costimulating polypeptide, wherein the chimeric costimulating polypeptide comprises two FKBP12 variant polypeptide regions and
 - i) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain; or
 - ii) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain, and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain.
2. The modified cell of claim 1, wherein the cell comprises a third polynucleotide encoding a chimeric antigen receptor or a recombinant T cell receptor.
3. A nucleic acid comprising a promoter operably linked to
 - a) a first polynucleotide encoding a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises
 - (i) a pro-apoptotic polypeptide region;
 - (ii) a FKBP12-Rapamycin-Binding (FRB) polypeptide region, or FRB variant polypeptide region; and
 - (iii) a FKBP12 polypeptide region; and
 - b) a second polynucleotide encoding a chimeric costimulating polypeptide, wherein the chimeric costimulating polypeptide comprises two FKBP12 variant polypeptide regions and
 - i) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain; or
 - ii) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain, and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain.

4. The nucleic acid of claim 3, wherein the promoter is operably linked to a third polynucleotide that encodes a chimeric antigen receptor or a recombinant T cell receptor.
5. A modified cell, comprising a nucleic acid of any one of claims 3 to 4.
6. The modified cell of any one of claims 1, 2, or 5, or the nucleic acid of any one of claims 3 or 4, wherein the chimeric costimulating polypeptide comprises a truncated MyD88 polypeptide region lacking the TIR domain and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain.
7. The modified cell of any one of claims 1, 2, 5, or 6, or the nucleic acid of any one of claims 3, 4, or 6, wherein the pro-apoptotic polypeptide is a Caspase-9 polypeptide that lacks the CARD domain.
8. The modified cell of any one of claims 1, 2, or 5 to 7, wherein the cell is a T cell, tumor infiltrating lymphocyte, NK-T cell, or NK cell.
9. Use of modified cells of any one of claims 1, 2, or 5 to 8 in the manufacture of a medicament for stimulating an immune response in a subject, wherein:
 - a) the modified cells are to be transplanted into the subject, and
 - b) after (a), an effective amount of a ligand that binds to the FKBP12 variant polypeptide region of the chimeric costimulating polypeptide is to be administered to stimulate a cell mediated immune response.
10. Use of a ligand that binds to the FKBP12 variant region of the chimeric costimulating polypeptide in the manufacture of a medicament for administering a ligand to a subject who has undergone cell therapy using modified cells, wherein the modified cells comprise modified cells of any one of claims 1, 2, or 5 to 8.
11. Use of a modified cell of any one of claims 1, 2, or 5 to 8 in the manufacture of a medicament for treating a subject having a disease or condition associated with an elevated expression of a target antigen expressed by a target cell, wherein:
 - a) an effective amount of the modified cells is to be transplanted into the subject; wherein the modified cell comprises a chimeric antigen receptor or a recombinant T cell receptor comprising an antigen recognition moiety that binds to the target antigen, and
 - b) after a), an effective amount of a ligand that binds to the FKBP12 variant polypeptide region of the chimeric costimulating polypeptide is to be administered to reduce the number or concentration of target antigen or target cells in the subject.

12. Use of a modified cell of any one of claims 1, 2, or 5 to 8 in the manufacture of a medicament for reducing the size of a tumor in a subject, wherein:

a) the modified cell of any one of claims 1, 2, or 5 to 8 is to be administered to the subject, wherein the cell comprises a chimeric antigen receptor or a recombinant T cell receptor comprising an antigen recognition moiety that binds to an antigen on the tumor; and

b) after a), an effective amount of a ligand that binds to the FKBP12 variant polypeptide region of the chimeric costimulating polypeptide is to be administered to reduce the size of the tumor in the subject.

13. Use of rapamycin or a rapalog that binds to the FRB polypeptide or FRB variant polypeptide region of the chimeric pro-apoptotic polypeptide in the manufacture of a medicament for controlling survival of transplanted modified cells in a subject, wherein:

a) modified cells of any one of claims 1, 2, or 5 to 8 are to be transplanted into the subject; and

b) after a), the rapamycin or rapalog is to be administered in an amount effective to kill at least 30% of the modified cells that express the chimeric pro-apoptotic polypeptide.

14. A modified cell comprising

a) a first polynucleotide encoding a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises

- i) a pro-apoptotic polypeptide region; and
- ii) a FKBP12 variant polypeptide region; and

b) a second polynucleotide encoding a chimeric costimulating polypeptide, wherein the chimeric costimulating polypeptide comprises

- i) a FKBP12-Rapamycin Binding (FRB) polypeptide region or FRB variant polypeptide region;
- ii) a FKBP12 polypeptide region; and
- iii) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain, or a MyD88 polypeptide region, or a truncated MyD88 polypeptide region lacking the TIR domain and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain.

15. The modified cell of claim 14, wherein the cell comprises a third polynucleotide, wherein the third polynucleotide encodes a chimeric antigen receptor or a recombinant T cell receptor.

16. A nucleic acid comprising a promoter operably linked to
- a) a first polynucleotide encoding a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises
 - i) a pro-apoptotic polypeptide region; and
 - ii) a FKBP12 variant polypeptide region; and
 - b) a second polynucleotide encoding a chimeric costimulating polypeptide, wherein the chimeric costimulating polypeptide comprises
 - i) a FKBP12-Rapamycin Binding (FRB) polypeptide region or FRB variant polypeptide region;
 - ii) a FKBP12 polypeptide region; and
 - iii) a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain, or a MyD88 polypeptide region or a truncated MyD88 polypeptide region lacking the TIR domain and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain.
17. The nucleic acid of claim 16, wherein the promoter is operably linked to a third polynucleotide that encodes chimeric antigen receptor or a recombinant T cell receptor.
18. A modified cell comprising a nucleic acid of any one of claims 16 to 17.
19. The modified cell of any one of claims 14 or 15, or the nucleic acid of any one of claims 16 or 17, wherein the chimeric costimulating polypeptide comprises a truncated MyD88 polypeptide region lacking the TIR domain and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain.
20. The modified cell of any one of claims 14, 15, 18, or 19, or the nucleic acid of any one of claims 16, 17 or 19, wherein the pro-apoptotic polypeptide is a Caspase-9 polypeptide that lacks CARD domain.
21. The modified cell of any one of claims 14, 15, or 18 to 20, wherein the cell is a T cell, tumor infiltrating lymphocyte, NK-T cell, or NK cell.
22. Use of modified cells of any one of claims 14, 15, or 18 to 21 in the manufacture of a medicament for stimulating an immune response in a subject, wherein:
- a) the modified cells are to be transplanted into the subject, and
 - b) after (a), an effective amount of a rapamycin or a rapalog that binds to the FRB polypeptide or FRB variant polypeptide region of the chimeric stimulating polypeptide is to be administered to stimulate a cell mediated immune response.

23. Use of rapamycin or a rapalog in the manufacture of a medicament for administering a ligand to a subject who has undergone cell therapy using modified cells, wherein the modified cells comprise modified cells of any one of claims 14, 15, or 18 to 21.
24. Use of a modified cell of any one of claims 14, 15, or 18 to 21 in the manufacture of a medicament for treating a subject having a disease or condition associated with an elevated expression of a target antigen expressed by a target cell, wherein:
- a) an effective amount of modified cells is to be transplanted into the subject; wherein the modified cell comprises a chimeric antigen receptor or a recombinant T cell receptor comprising an antigen recognition moiety that binds to the target antigen, and
 - b) after a), an effective amount of rapamycin or a rapalog that binds to the FRB polypeptide or FRB variant region of the chimeric stimulating polypeptide is to be administered to reduce the number or concentration of target antigen or target cells in the subject.
25. Use of a modified cell of any one of claims 14, 15, or 18 to 21 in the manufacture of a medicament for reducing the size of a tumor in a subject, wherein:
- a) the modified cell of any one of claims 14, 15, or 18 to 21 is to be administered to the subject, wherein the cell comprises a chimeric antigen receptor or a recombinant T cell receptor comprising an antigen recognition moiety that binds to an antigen on the tumor; and
 - b) after a), an effective amount of rapamycin or a rapalog that binds to the FRB or FRB variant polypeptide region of the chimeric stimulating polypeptide is to be administered to reduce the size of the tumor in the subject.
26. Use of a ligand that binds to the FKBP12 variant polypeptide region of the chimeric pro-apoptotic polypeptide in the manufacture of a medicament for controlling survival of transplanted modified cells in a subject, wherein:
- a) the modified cells of any one of claims 14, 15, or 18 to 21 are to be transplanted into the subject, and
 - b) after (a), the ligand is to be administered in an amount effective to kill at least 90% of the modified cells that express the chimeric pro-apoptotic polypeptide.
27. A nucleic acid comprising a promoter operably linked to a polynucleotide coding for a chimeric pro-apoptotic polypeptide, wherein the chimeric pro-apoptotic polypeptide comprises

- a) a pro-apoptotic polypeptide region;
- b) a FKBP12-Rapamycin binding (FRB) polypeptide region or FRB variant polypeptide region; and
- c) a FKBP12 variant polypeptide region.