In a **twefth** 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 in need of treatment with said modified cells, 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 costimulating polypeptide is to be administered to said subject, wherein rapamycin or the rapalog causes the chimeric costimulating polypeptide to dimerize or multimerize, thereby activating the modified cells, wherein the modified cells stimulate a cell mediated immune response, and wherein the modified cells are T cells, tumor infiltrating lymphocytes, NK-T cells, or NK cells.

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, wherein rapamycin or the rapalog causes the chimeric costimulating polypeptide to dimerize or multimerize, thereby activating the modified cells, wherein the modified cells stimulate a cell mediated immune response, and wherein the modified cells are T cells, tumor infiltrating lymphocytes, NK-T cells, or NK cells.

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 costimulating polypeptide is to be administered to reduce the number or concentration of target antigen or target cells in the subject, wherein the modified cells are T cells, tumor infiltrating lymphocytes, NK-T cells, or NK cells.

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 costimulating polypeptide is to be administered to reduce the size of the tumor in the subject, wherein the modified cells are T cells, tumor infiltrating lymphocytes, NK-T cells, or NK cells.

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.

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,

wherein upon contacting the modified cell with rapamycin or a rapalog, the chimeric pro-apoptotic polypeptide dimerizes or multimerizes, thereby inducing apoptosis of the modified cell; and upon contacting the modified cell with rimiducid, the chimeric costimulating polypeptide dimerizes or multimerizes, thereby activating the modified cell.

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,

wherein upon contacting the chimeric pro-apoptotic polypeptide encoded by said first polynucleotide with rapamycin or a rapalog, the chimeric pro-apoptotic polypeptide dimerizes or multimerizes; and upon contacting the chimeric costimulating polypeptide encoded by said second polynucleotide with rimiducid, the chimeric costimulating polypeptide dimerizes or multimerizes.

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 claim 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 in need of treatment with said modified cells, 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 said subject, wherein the ligand that binds to the FKBP12 variant polypeptide region causes the chimeric costimulating polypeptide to dimerize or multimerize, thereby activating the modified cells, wherein the modified cells stimulate a cell mediated immune response, and wherein the modified cells are T cells, tumor infiltrating lymphocytes, NK-T cells, or NK cells.

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, wherein the ligand that binds to the FKBP12 variant polypeptide region causes the chimeric costimulating polypeptide to dimerize or multimerize, thereby activating the modified cells, wherein the modified cells stimulate a cell mediated immune response, and wherein the modified cells are T cells, tumor infiltrating lymphocytes, NK-T cells, or NK cells.

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,

wherein the modified cells are T cells, tumor infiltrating lymphocytes, NK-T cells, or NK cells.

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,

wherein the modified cells are T cells, tumor infiltrating lymphocytes, NK-T cells, or NK cells.

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,

wherein upon contacting the modified cell with rimiducid, the chimeric pro-apoptotic polypeptide dimerizes or multimerizes, thereby inducing apoptosis of the modified cell; and upon contacting the modified cell with rapamycin or a rapalog, the chimeric costimulating polypeptide dimerizes or multimerizes, thereby activating the modified cell.

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,

wherein upon contacting the chimeric pro-apoptotic polypeptide encoded by said first polynucleotide with rimiducid, the chimeric pro-apoptotic polypeptide dimerizes or multimerizes; and upon contacting the chimeric costimulating polypeptide encoded by said second polynucleotide with rapamycin or a rapalog, the chimeric costimulating polypeptide, dimerizes or multimerizes.

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 claim 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 in need of treatment with said modified cells, 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 costimulating polypeptide is to be administered to said subject, wherein rapamycin or the rapalog causes the chimeric costimulating polypeptide to dimerize or multimerize, thereby activating the modified cells, wherein the modified cells stimulate a cell mediated

immune response, and wherein the modified cells are T cells, tumor infiltrating lymphocytes, NK-T cells, or NK cells.

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, wherein rapamycin or the rapalog causes the chimeric costimulating polypeptide to dimerize or multimerize, thereby activating the modified cells, wherein the modified cells stimulate a cell mediated immune response, and wherein the modified cells are T cells, tumor infiltrating lymphocytes, NK-T cells, or NK cells.

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 costimulating polypeptide is to be administered to reduce the number or concentration of target antigen or target cells in the subject,

wherein the modified cells are T cells, tumor infiltrating lymphocytes, NK-T cells, or NK cells.

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 costimulating polypeptide is to be administered to reduce the size of the tumor in the subject,

wherein the modified cells are T cells, tumor infiltrating lymphocytes, NK-T cells, or NK cells.

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.