

acids and/or expression cassettes and vectors are provided. Also provided, are methods of treating a subject using the described components and methods as well as kits for practicing the subject methods.

[0006] The instant disclosure includes a chimeric polypeptide comprising, from N-terminal to C-terminal and in covalent linkage: a) an extracellular domain comprising a specific binding member that specifically binds to a peptide-major histocompatibility complex (peptide-MHC); b) a proteolytically cleavable Notch receptor polypeptide comprising one or more proteolytic cleavage sites; and c) an intracellular domain comprising a transcriptional activator or repressor, wherein binding of the specific binding member to the peptide-MHC induces cleavage of the Notch receptor polypeptide at the one or more proteolytic cleavage sites, thereby releasing the intracellular domain.

[0006a] In one aspect, there is provided a chimeric polypeptide comprising, from N-terminal to C-terminal and in covalent linkage:

a) an extracellular domain comprising a specific binding member that specifically binds to a peptide-major histocompatibility complex (peptide-MHC);

b) a proteolytically cleavable Notch receptor polypeptide comprising one or more proteolytic cleavage sites; and

c) an intracellular domain comprising a transcriptional activator, wherein binding of the specific binding member to the peptide-MHC induces cleavage of the Notch receptor polypeptide at the one or more proteolytic cleavage sites, thereby releasing the intracellular domain.

[0007] In some embodiments, the specific binding member comprises an antibody. In some embodiments, the antibody is a nanobody, a diabody, a triabody, or a minibody, a F(ab')₂ fragment, a Fab fragment, a single chain variable fragment (scFv) or a single domain antibody (sdAb).

[0008] In some embodiments, the specific binding member specifically binds a peptide-MHC comprising an intracellular cancer antigen peptide. In some embodiments, the intracellular cancer antigen peptide is a WT1 peptide or a NY-ESO peptide.

[0009] In some embodiments, the Notch receptor polypeptide comprises, at its N-terminus, one or more epidermal growth factor (EGF) repeats. In some embodiments, the Notch receptor polypeptide comprises, at its N-terminus, 2 to 11 EGF repeats. In some embodiments, the Notch receptor polypeptide comprises a synthetic linker. In some embodiments, the Notch receptor polypeptide comprises a synthetic linker between the one or more EGF repeats and the one or more proteolytic cleavage sites. In some embodiments, the Notch receptor polypeptide has a length from 50 amino acids to 1000 amino acids. In some embodiments, the Notch receptor polypeptide has a length from 300 amino acids to 400 amino acids. In some embodiments, the one or more proteolytic cleavage sites comprises an S2 proteolytic cleavage site, an S3 proteolytic cleavage site or a combination thereof. In some embodiments, the one or more proteolytic cleavage sites comprises an S2 proteolytic cleavage site that is an ADAM family type protease cleavage site, such as e.g., an ADAM-17-type protease cleavage site comprising an Ala-Val dipeptide sequence. In some embodiments, the one or more proteolytic cleavage sites comprises an S3 proteolytic cleavage site that is a gamma-secretase (γ -secretase) cleavage site comprising a Gly-Val dipeptide sequence. In some embodiments, the one or more proteolytic cleavage sites further comprises an S1 proteolytic cleavage site. In some embodiments, the S1 proteolytic cleavage site is a furin-like protease cleavage site comprising the amino acid sequence Arg-X-(Arg/Lys)-Arg (SEQ ID NO:130), where X is any amino acid. In some embodiments, the Notch receptor polypeptide lacks an S1 proteolytic cleavage site. In some embodiments, the Notch receptor polypeptide has at least 85% amino acid sequence identity to a sequence provided in FIG. 31A-32B. In some embodiments, the Notch

receptor polypeptide has at least 85% amino acid sequence identity to the sequence provided in FIG. 31A or the sequence provided in FIG. 31B.

[0010] Aspects of the instant disclosure include a nucleic acid encoding any of the above described chimeric polypeptides.

[0011] In some embodiments, the nucleic acid further comprises a transcriptional control element responsive to the transcriptional activator or repressor operably linked to a nucleic acid sequence encoding a polypeptide of interest (POI). In some embodiments, the POI is a heterologous polypeptide selected from the group consisting of: a reporter protein, a chimeric antigen receptor (CAR), an antibody, a chimeric bispecific binding member, an engineered T cell receptor (TCR) and an innate-immune response inducer.

[0012] Aspects of the instant disclosure include a recombinant expression vector comprising any of the above described nucleic acids.

[0013] The instant disclosure includes a method of inducing expression of a heterologous polypeptide in a cell, the method comprising: contacting a cell with a peptide-major histocompatibility complex (peptide-MHC), wherein the cell expresses any of the chimeric polypeptides described above and comprises a sequence encoding the heterologous polypeptide operably linked to a transcriptional control element responsive to a transcriptional activator of the chimeric polypeptide, thereby releasing the intracellular domain of the chimeric polypeptide and inducing expression of the heterologous polypeptide.

[0014] In some embodiments, the heterologous polypeptide is a reporter protein, a chimeric antigen receptor (CAR), an antibody, a chimeric bispecific binding member, an engineered T cell receptor (TCR) and an innate-immune response inducer.

[0014a] In one aspect, there is provided a method of inducing expression of a heterologous polypeptide in a cell, the method comprising:

contacting a cell with a peptide-major histocompatibility complex (peptide-MHC), wherein the cell expresses any of the chimeric polypeptides described above and comprises a sequence encoding the heterologous polypeptide operably linked to a transcriptional control element responsive to the transcriptional activator of the chimeric polypeptide, thereby releasing the intracellular domain of the chimeric polypeptide and inducing expression of the heterologous polypeptide, optionally wherein the heterologous polypeptide is a reporter protein, a chimeric antigen receptor (CAR), an antibody, a chimeric bispecific binding member, an engineered T cell receptor (TCR) and an innate-immune response inducer.

[0015] The instant disclosure includes a host cell comprising: a) a nucleic acid encoding any of the chimeric polypeptides described above that specifically binds to a first peptide-major histocompatibility complex (peptide-MHC); and b) a transcriptional control element responsive to a transcriptional activator of the chimeric polypeptide operably linked to a nucleic acid encoding a polypeptide of interest (POI).

[0016] In some embodiments, the host cell is genetically modified and the nucleic acid and the transcriptional control element are present within the genome of the host cell. In some embodiments, the nucleic acid and the transcriptional control element are present extrachromosomally within the host cell. In some embodiments, the POI is a heterologous polypeptide. In some embodiments, the heterologous polypeptide is selected from the group consisting of: a reporter protein, a chimeric antigen receptor (CAR), an antibody, a chimeric bispecific binding member, an engineered T cell receptor (TCR) and an innate-immune response inducer.

[0016a] In one aspect, there is provided a host cell comprising:

a) a nucleic acid encoding any of the chimeric polypeptides described above that specifically binds to a first peptide-major histocompatibility complex (peptide-MHC); and

b) a transcriptional control element responsive to the transcriptional activator of the chimeric polypeptide operably linked to a nucleic acid encoding a polypeptide of interest (POI), optionally wherein:

the host cell is genetically modified and the nucleic acid and the transcriptional control element are present within the genome of the host cell; the nucleic acid and the transcriptional control element are present extrachromosomally within the host cell; or the POI is a heterologous polypeptide, optionally selected from the group consisting of: a reporter protein, a chimeric antigen receptor (CAR), an antibody, a chimeric bispecific binding member, an engineered T cell receptor (TCR) and an innate-immune response inducer. In some embodiments, the heterologous polypeptide is a CAR that

embodiments, the target molecule is a tissue specific molecule. In some embodiments, the target molecule is an organ specific molecule. In some embodiments, the target molecule is a cell type specific molecule.

[0019] The instant disclosure includes a method of treating a subject for a neoplasia comprising administering to the subject an effective amount of host cells according to any of those described above, wherein the neoplasia expresses the target molecule and the cancer antigen. In one aspect, there is provided use of an effective amount of host cells according to any of those described above, in the manufacture of a medicament for treating a subject for a neoplasia, wherein the neoplasia expresses the target molecule and the cancer antigen.

[0020] Aspects of the instant disclosure include a host cell comprising: a) a nucleic acid encoding a chimeric polypeptide comprising, from N-terminal to C-terminal and in covalent linkage: i) an extracellular domain comprising a specific binding member that specifically binds to a target molecule present on the surface of a cancer cell; ii) a proteolytically cleavable Notch receptor polypeptide comprising one or more proteolytic cleavage sites; and iii) an intracellular domain comprising a transcriptional activator; b) a nucleic acid encoding an anti-Fc chimeric antigen receptor (CAR) operably linked to a transcriptional control element responsive to the transcriptional activator, wherein binding of the specific binding member to the target molecule induces cleavage of the Notch receptor polypeptide at the one or more proteolytic cleavage sites, thereby releasing the intracellular domain, activating the transcriptional control element and causing the anti-Fc CAR to be expressed.

[0021] In some embodiments, the target molecule is a cancer antigen. In some embodiments, the target molecule is a tissue specific molecule. In some embodiments, the target molecule is an organ specific molecule. In some embodiments, the target molecule is a cell type specific molecule. In some embodiments, the host cell further comprises a nucleic acid encoding an antibody specific for a cancer antigen present on the surface of a cancer cell and comprising an Fc region that is bound by the anti-Fc CAR. In some embodiments, the nucleic acid encoding the antibody is operably linked to the transcriptional control element.

[0022] The instant disclosure includes, a method of treating a subject for a neoplasia comprising administering to the subject an effective amount of any of the host cells described above, wherein the neoplasia expresses the target molecule.

[0023] In some embodiments, the method further comprises administering to the subject an antibody specific for a cancer antigen present on the surface of a cancer cell and comprising an Fc region that is bound by the anti-Fc CAR. In one aspect, there is provided use of an effective amount of any of the host cells described above, in the manufacture of a medicament for treating a subject for a neoplasia, wherein the neoplasia expresses the target molecule, optionally wherein the medicament is to be administered to the subject with an antibody specific for a cancer antigen present on the surface of a cancer cell and comprising an Fc region that is bound by the anti-Fc CAR.

[0024] Aspects of the instant disclosure include a host cell comprising: a) a nucleic acid encoding a chimeric polypeptide comprising, from N-terminal to C-terminal and in covalent linkage: i) an extracellular domain comprising a specific binding member that specifically binds to a target molecule present on the surface of a cancer cell; ii) a proteolytically cleavable Notch receptor polypeptide comprising one or more proteolytic cleavage sites; and iii) an intracellular domain comprising a

transcriptional activator; b) a nucleic acid encoding an innate-immune response inducer operably linked to a transcriptional control element responsive to the transcriptional activator, wherein binding of the specific binding member to the target molecule induces cleavage of the Notch receptor polypeptide at the one or more proteolytic cleavage sites, thereby releasing the intracellular domain, activating the transcriptional control element and causing the innate-immune response inducer to be expressed.

[0025] In some embodiments, the target molecule is a tissue specific molecule. In some embodiments, the target molecule is an organ specific molecule. In some embodiments, the target molecule is a cell type specific molecule. In some embodiments, the target molecule is a cancer antigen. In some embodiments, the innate-immune response inducer is bacterial protein or fragment thereof. In some embodiments, the innate-immune response inducer is viral protein or fragment thereof. In some embodiments, the innate-immune response inducer is fungal protein or fragment thereof. In some embodiments, the innate-immune response inducer is a protein or fragment thereof expressed by a mammalian parasite. In some embodiments, the mammalian parasite is a human parasite.

[0026] The instant disclosure includes a method of inducing a local innate immune response in an area of a subject, the method comprising administering to the subject an effective amount of those host cells described above, wherein the area expresses the target molecule. In some embodiments, the area of the subject comprises a neoplasia. In one aspect, there is provided use of an effective amount of those host cells described above, in the manufacture of a medicament for inducing a local innate immune response in an area of a subject, wherein the area expresses the target molecule, optionally wherein the area of the subject comprises a neoplasia.

[0027] Aspects of the instant disclosure include a host cell comprising: a) a nucleic acid encoding a chimeric polypeptide comprising, from N-terminal to C-terminal and in covalent linkage: i) an extracellular domain comprising a specific binding member that specifically binds to a target molecule present on the surface of a cancer cell; ii) a proteolytically cleavable Notch receptor polypeptide comprising one or more proteolytic cleavage sites; and iii) an intracellular domain comprising a transcriptional activator; b) a nucleic acid encoding an immune suppression factor operably linked to a transcriptional control element responsive to the transcriptional activator, wherein binding of the specific binding member to the target molecule induces cleavage of the Notch receptor polypeptide at the one or more proteolytic cleavage sites, thereby releasing the intracellular domain, activating the transcriptional control element and causing the immune suppression factor to be expressed.

[0028] In some embodiments, the target molecule is a tissue specific molecule. In some embodiments, the target molecule is an organ specific molecule. In some embodiments, the target molecule is a cell type specific molecule. In some embodiments, the target molecule is an autoantigen. In some embodiments, the immune suppression factor is an immunosuppressive cytokine. In some embodiments, the immunosuppressive cytokine is IL-10. In some embodiments, the immune suppression factor is a cell-to-cell signaling immunosuppressive ligand. In some embodiments, the cell-to-cell signaling immunosuppressive ligand is PD-L1.

[0029] The instant disclosure includes a method of suppressing an immune response in a subject, the method comprising administering to the subject an effective amount of any of the host cells described above, wherein the subject expresses the target molecule. In some embodiments, the subject has an autoimmune disease. In one aspect, there is provided use of an effective amount of any of the host cells described above, in the manufacture of a medicament for suppressing an immune response in a subject, wherein the subject expresses the target molecule, optionally wherein the subject has an autoimmune disease.

[0030] Aspects of the instant disclosure include a method of killing a heterogeneous tumor, the method comprising: contacting a heterogeneous tumor comprising a first cell expressing a killing antigen and a second cell expressing the killing antigen and a priming antigen with an engineered immune cell comprising: a proteolytically cleavable chimeric polypeptide that specifically binds the priming antigen; a nucleic acid sequence encoding a therapeutic polypeptide that specifically binds the killing antigen; and a transcriptional control element operably linked to the nucleic acid that is responsive to the proteolytically cleavable chimeric polypeptide, wherein binding of the proteolytically cleavable chimeric polypeptide to the priming antigen activates the transcriptional control element to induce expression of the therapeutic polypeptide which, when bound to the killing antigen, kills the first and second cells of the heterogeneous tumor.

[0031] In some embodiments, the therapeutic polypeptide is a chimeric antigen receptor (CAR). In some embodiments, the therapeutic polypeptide is a T cell Receptor (TCR). In some embodiments, the therapeutic polypeptide is a therapeutic antibody. In some embodiments, the therapeutic polypeptide is a chimeric bispecific binding member. In some embodiments, at least one of the priming antigen or the killing antigen is an intracellular antigen presented in the context of MHC. In some embodiments, both the priming antigen and the killing antigen are intracellular antigens presented in the context of MHC.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] **FIG. 1** schematically depicts specific binding of an embodiment of a proteolytically cleavable chimeric polypeptide (synNotch) expressed on a receiver cell with a major histocompatibility complex (MHC)-presented antigen of a sender cell to induce expression of a gene or coding sequence ("X") in the receiver cell.

[0033] **FIG. 2** demonstrates the specific expression of blue fluorescent protein (BFP) reporter in receiver cells expressing a proteolytically cleavable chimeric polypeptide according to one embodiment described herein, as generally depicted in **FIG. 1**, specific for MHC-presented WT1 antigen. The reporter is expressed when receiver cells were contacted with sender cells expressing the MHC-presented WT1 antigen but not when contacted with sender cells that do not express the antigen.

[0034] **FIG. 3** provides quantification related to **FIG. 2** showing WT1 intracellular antigen dependent activation of the proteolytically cleavable chimeric polypeptide.

CLAIMS

What is claimed is:

1. A chimeric polypeptide comprising, from N-terminal to C-terminal and in covalent linkage:
 - a) an extracellular domain comprising a specific binding member that specifically binds to a peptide-major histocompatibility complex (peptide-MHC);
 - b) a proteolytically cleavable Notch receptor polypeptide comprising one or more proteolytic cleavage sites; and
 - c) an intracellular domain comprising a transcriptional activator, wherein binding of the specific binding member to the peptide-MHC induces cleavage of the Notch receptor polypeptide at the one or more proteolytic cleavage sites, thereby releasing the intracellular domain.
2. The chimeric polypeptide of Claim 1, wherein the specific binding member comprises an antibody optionally wherein the antibody is a nanobody, a diabody, a triabody, or a minibody, a F(ab')₂ fragment, a Fab fragment, a single chain variable fragment (scFv) or a single domain antibody (sdAb).
3. The chimeric polypeptide of any of the preceding claims, wherein the specific binding member specifically binds a peptide-MHC comprising an intracellular cancer antigen peptide, optionally wherein the intracellular cancer antigen peptide is a WT1 peptide or a NY-ESO peptide.
4. The chimeric polypeptide of any of the preceding claims, wherein the Notch receptor polypeptide comprises:
 - one or more epidermal growth factor (EGF) repeats at its N-terminus, optionally 2 to 11 EGF repeats; a synthetic linker, optionally
 - a synthetic linker between the one or more EGF repeats and the one or more proteolytic cleavage sites; a length from 50 amino acids to 1000 amino acids, optionally from 300 amino acids to 400 amino acids; an S2 proteolytic cleavage site, an S3 proteolytic cleavage site or a combination thereof, optionally an S2 proteolytic cleavage site that is an ADAM-17-type protease cleavage site comprising an Ala-Val dipeptide sequence, an S3 proteolytic cleavage site that is a

gamma-secretase (γ -secretase) cleavage site comprising a Gly-Val dipeptide sequence, or a combination thereof; or

a combination thereof.

5. The chimeric polypeptide of any of the preceding claims, wherein the Notch receptor polypeptide has at least 85% amino acid sequence identity to a sequence provided in FIG. 31A-32B, optionally at least 85% amino acid sequence identity to the sequence provided in FIG. 31A or the sequence provided in FIG. 31B.

6. A nucleic acid encoding the chimeric polypeptide according to any of Claims 1-5.

7. The nucleic acid of Claim 6, wherein the nucleic acid further comprises a transcriptional control element responsive to the transcriptional activator operably linked to a nucleic acid sequence encoding a polypeptide of interest (POI), optionally wherein the POI is a heterologous polypeptide selected from the group consisting of: a reporter protein, a chimeric antigen receptor (CAR), an antibody, a chimeric bispecific binding member, an engineered T cell receptor (TCR) and an innate-immune response inducer.

8. A recombinant expression vector comprising the nucleic acid according to Claim 6 or 7.

9. A method of inducing expression of a heterologous polypeptide in a cell, the method comprising:

contacting a cell with a peptide-major histocompatibility complex (peptide-MHC), wherein the cell expresses a chimeric polypeptide according to any of Claims 1-5 and comprises a sequence encoding the heterologous polypeptide operably linked to a transcriptional control element responsive to the transcriptional activator of the chimeric polypeptide, thereby releasing the intracellular domain of the chimeric polypeptide and inducing expression of the heterologous polypeptide, optionally wherein the heterologous polypeptide is a reporter protein, a chimeric antigen receptor (CAR), an antibody, a chimeric bispecific binding member, an engineered T cell receptor (TCR) and an innate-immune response inducer.

10. A host cell comprising:

a) a nucleic acid encoding a chimeric polypeptide according to Claim 6 or 7 that specifically binds to a first peptide-major histocompatibility complex (peptide-MHC); and

b) a transcriptional control element responsive to the transcriptional activator of the chimeric polypeptide operably linked to a nucleic acid encoding a polypeptide of interest (POI), optionally wherein:

the host cell is genetically modified and the nucleic acid and the transcriptional control element are present within the genome of the host cell; the nucleic acid and the transcriptional control element are present extrachromosomally within the host cell; or the POI is a heterologous polypeptide, optionally selected from the group consisting of: a reporter protein, a chimeric antigen receptor (CAR), an antibody, a chimeric bispecific binding member, an engineered T cell receptor (TCR) and an innate-immune response inducer.

11. The host cell of Claim 10, wherein the POI is a heterologous polypeptide that is a CAR that specifically binds to a second peptide-MHC, optionally wherein the specific binding member of the chimeric polypeptide specifically binds to a first peptide-MHC comprising a first intracellular cancer antigen peptide and the CAR specifically binds to a second peptide-MHC comprising a second intracellular cancer antigen peptide.

12. The host cell of Claim 11, wherein the first intracellular cancer antigen peptide is a WT1 peptide and the second intracellular cancer antigen peptide is a NY-ESO peptide, or the first intracellular cancer antigen peptide is a NY-ESO peptide and the second intracellular cancer antigen peptide is a WT1 peptide.

13. The host cell of Claim 10, wherein the heterologous polypeptide is an engineered TCR that specifically binds to a second peptide-MHC, optionally wherein the specific binding member of the chimeric polypeptide specifically binds to a first peptide-MHC comprising a first intracellular cancer antigen peptide and the engineered TCR specifically binds to a second peptide-MHC comprising a second intracellular cancer antigen peptide.

14. The host cell of Claim 13, wherein the first intracellular cancer antigen peptide is a WT1 peptide and the second intracellular cancer antigen peptide is a NY-ESO peptide, or the first intracellular cancer antigen peptide is a NY-ESO peptide and the second intracellular cancer antigen peptide is a WT1 peptide.

15. A host cell comprising:
a) a nucleic acid encoding a chimeric polypeptide comprising, from N-terminal to C-terminal and in covalent linkage:
i) an extracellular domain comprising a specific binding member that specifically binds to a target molecule present on the surface of a cancer cell;
ii) a proteolytically cleavable Notch receptor polypeptide comprising one or more proteolytic cleavage sites; and
iii) an intracellular domain comprising a transcriptional activator;
b) a nucleic acid encoding a chimeric bispecific binding member operably linked to a transcriptional control element responsive to the transcriptional activator, wherein binding of the specific binding member to the target molecule induces cleavage of the Notch receptor polypeptide at the one or more proteolytic cleavage sites, thereby releasing the intracellular domain, activating the transcriptional control element and causing the chimeric bispecific binding member to be expressed.

16. The host cell according to Claim 15, wherein the chimeric bispecific binding member comprises a binding domain specific for a cancer antigen and a binding domain specific for a protein expressed on the surface of an immune cell, optionally wherein:

the chimeric bispecific binding member comprises at least one antibody derived antigen-binding domains, optionally wherein the chimeric bispecific binding member is a bispecific antibody or a fragment thereof; the chimeric bispecific binding member comprises at least one receptor or ligand binding domain of a ligand-receptor binding pair; or the chimeric bispecific binding member comprises at least one antibody derived antigen-binding domain and at least one receptor or ligand binding domain of a ligand-receptor binding pair.

17. The host cell according to Claim 15 or 16, wherein the protein expressed on the surface of an immune cell is CD3 or Natural Killer Group 2D (NKG2D) receptor, optionally wherein the target molecule is a cancer antigen, a tissue specific molecule, an organ specific molecule, or a cell type specific molecule.

18. Use of an effective amount of host cells according to any of Claims 15-17, in the manufacture of a medicament for treating a subject for a neoplasia, wherein the neoplasia expresses the target molecule and the cancer antigen.

19. A host cell comprising:
- a) a nucleic acid encoding a chimeric polypeptide comprising, from N-terminal to C-terminal and in covalent linkage:
 - i) an extracellular domain comprising a specific binding member that specifically binds to a target molecule present on the surface of a cancer cell;
 - ii) a proteolytically cleavable Notch receptor polypeptide comprising one or more proteolytic cleavage sites; and
 - iii) an intracellular domain comprising a transcriptional activator;
 - b) a nucleic acid encoding an anti-Fc chimeric antigen receptor (CAR) operably linked to a transcriptional control element responsive to the transcriptional activator, wherein binding of the specific binding member to the target molecule induces cleavage of the Notch receptor polypeptide at the one or more proteolytic cleavage sites, thereby releasing the intracellular domain, activating the transcriptional control element and causing the anti-Fc CAR to be expressed.
20. The host cell of Claim 19, wherein the target molecule is a cancer antigen, a tissue specific molecule, an organ specific molecule, or a cell type specific molecule.
21. The host cell of Claim 19 or 20, wherein the host cell further comprises a nucleic acid encoding an antibody specific for a cancer antigen present on the surface of a cancer cell and comprising an Fc region that is bound by the anti-Fc CAR, optionally wherein the nucleic acid encoding the antibody is operably linked to the transcriptional control element.
22. Use of an effective amount of host cells according to any of Claims 19-21, in the manufacture of a medicament for treating a subject for a neoplasia, wherein the neoplasia expresses the target molecule, optionally wherein the medicament is to be administered to the subject with an antibody specific for a cancer antigen present on the surface of a cancer cell and comprising an Fc region that is bound by the anti-Fc CAR.
23. A host cell comprising:
- a) a nucleic acid encoding a chimeric polypeptide comprising, from N-terminal to C-terminal and in covalent linkage:
 - i) an extracellular domain comprising a specific binding member that specifically binds to a target molecule present on the surface of a cancer cell;

- ii) a proteolytically cleavable Notch receptor polypeptide comprising one or more proteolytic cleavage sites; and
- iii) an intracellular domain comprising a transcriptional activator;
- b) a nucleic acid encoding an innate-immune response inducer operably linked to a transcriptional control element responsive to the transcriptional activator, wherein binding of the specific binding member to the target molecule induces cleavage of the Notch receptor polypeptide at the one or more proteolytic cleavage sites, thereby releasing the intracellular domain, activating the transcriptional control element and causing the innate-immune response inducer to be expressed.

24. The host cell of Claim 23, wherein the target molecule is a tissue specific molecule, an organ specific molecule, a cell type specific molecule, or a cancer antigen, optionally wherein the innate-immune response inducer is bacterial protein or fragment thereof, a viral protein or fragment thereof, a fungal protein or fragment thereof, or a protein or fragment thereof expressed by a mammalian parasite, optionally a human parasite.

25. Use of an effective amount of host cells according to Claim 23 or 24, in the manufacture of a medicament for inducing a local innate immune response in an area of a subject, wherein the area expresses the target molecule, optionally wherein the area of the subject comprises a neoplasia.

26. A host cell comprising:

- a) a nucleic acid encoding a chimeric polypeptide comprising, from N-terminal to C-terminal and in covalent linkage:
 - i) an extracellular domain comprising a specific binding member that specifically binds to a target molecule present on the surface of a cancer cell;
 - ii) a proteolytically cleavable Notch receptor polypeptide comprising one or more proteolytic cleavage sites; and
 - iii) an intracellular domain comprising a transcriptional activator;
- b) a nucleic acid encoding an immune suppression factor operably linked to a transcriptional control element responsive to the transcriptional activator, wherein binding of the specific binding member to the target molecule induces cleavage of the Notch receptor polypeptide at the one or more proteolytic cleavage sites, thereby releasing the intracellular

domain, activating the transcriptional control element and causing the immune suppression factor to be expressed.

27. The host cell of Claim 26, wherein the target molecule is a tissue specific molecule, an organ specific molecule, a cell type specific molecule or an autoantigen, optionally wherein the immune suppression factor is an immunosuppressive cytokine, optionally IL-10, or a cell-to-cell signaling immunosuppressive ligand, optionally PD-L1.

28. Use of an effective amount of host cells according to Claim 26 or 27, in the manufacture of a medicament for suppressing an immune response in a subject, wherein the subject expresses the target molecule, optionally wherein the subject has an autoimmune disease.

29. A method of killing a heterogeneous tumor, the method comprising:
contacting a heterogeneous tumor comprising a first cell expressing a killing antigen and a second cell expressing the killing antigen and a priming antigen with an engineered immune cell comprising:

a proteolytically cleavable chimeric polypeptide that specifically binds the priming antigen;

a nucleic acid sequence encoding a therapeutic polypeptide that specifically binds the killing antigen; and

a transcriptional control element operably linked to the nucleic acid that is responsive to the proteolytically cleavable chimeric polypeptide,

wherein binding of the proteolytically cleavable chimeric polypeptide to the priming antigen activates the transcriptional control element to induce expression of the therapeutic polypeptide which, when bound to the killing antigen, kills the first and second cells of the heterogeneous tumor.

30. The method of Claim 29, wherein the therapeutic polypeptide is a chimeric antigen receptor (CAR), a T cell Receptor (TCR), a therapeutic antibody, or a chimeric bispecific binding member, optionally wherein at least one of the priming antigen or the killing antigen is an intracellular antigen presented in the context of MHC, optionally wherein both the priming antigen and the killing antigen are intracellular antigens presented in the context of MHC.