

CLAIMS

1. A composition comprising an effector module, said effector module comprising a stimulus response element (SRE) and at least one payload which is operably linked to said SRE, wherein the SRE comprises a destabilizing domain (DD), said DD comprising, in whole or in part, a cGMP-specific 3',5'-cyclic phosphodiesterase (hPDE5; SEQ ID NO.1) which is capable of ligand binding, and further comprising a mutation in the amino acid at position 732 (R732) of SEQ ID NO: 1.
2. A composition comprising an effector module, said effector module comprising a stimulus response element (SRE) and at least one payload which is operably linked to said SRE, wherein the SRE comprises a destabilizing domain (DD), wherein the DD comprises the catalytic domain of hPDE5 (SEQ ID NO: 3) which is capable of ligand binding, and comprises a mutation in the amino acid at the position corresponding to amino acid 732 (R732) of SEQ ID NO: 1.
3. The composition of claim 2, wherein the mutation in the amino acid at position 732 (R732) is selected from the group consisting of R732L, R732A, R732G, R732V, R732I, R732P, R732F, R732W, R732Y, R732H, R732S, R732T, R732D, R732E, R732Q, R732N, R732M, R732C, and R732K.
4. The composition of claim 3, wherein the mutation in the amino acid at position R732 is R732L.
5. The composition of claim 2, wherein the DD further comprises a mutation in the amino acid at the position corresponding to amino acid 764 (D764) of SEQ ID NO: 1, wherein the mutation at D764 is selected from the group consisting of D764N and D764A.
6. The composition of claim 2, wherein the DD further comprises a mutation in the amino acid at the position corresponding to amino acid 612 (Y612) of SEQ ID NO: 1, wherein the mutation at Y612 is selected from the group consisting of Y612A, Y612F, and Y612W.
7. The composition of claim 2, wherein the DD further comprises an F736A mutation in the amino acid at the position corresponding to amino acid 736 (F736) of SEQ ID NO: 1.

8. The composition of claim 2, wherein the DD further comprises an H653A mutation in the amino acid at the position corresponding to amino acid 653 (H653) of SEQ ID NO: 1.
9. The composition of claim 2, wherein the at least one payload is an immunotherapeutic agent.
10. The composition of claim 9, wherein the immunotherapeutic agent is selected from a chimeric antigen receptor (CAR) and a cytokine-cytokine receptor fusion polypeptide.
11. The composition of claim 10, wherein the immunotherapeutic agent is a chimeric antigen receptor (CAR) that comprises
- (a) an extracellular target moiety;
 - (b) a transmembrane domain;
 - (c) an intracellular signaling domain; and
 - (d) optionally, one or more co-stimulatory domains.
12. The composition of claim 11, wherein the extracellular target moiety is a scFv derived from an antibody that specifically recognizes a CD 19 target molecule.
13. The composition of claim 10, wherein the immunotherapeutic agent is a cytokine-cytokine receptor fusion polypeptide that comprises the whole or a portion of IL15, fused to the whole or a portion of IL15Ra to produce a IL15-IL15Ra fusion polypeptide.
14. The composition of claim 2, wherein the SRE is responsive to one or more stimuli, and wherein said one or more stimuli is selected from Tadalafil, Vardenafil, Sildenafil, Avanafil, Lodenafil, Mirodenafil, Udenafil, Benzamidenafil, Dasantafil, and Beminafil.
15. A pharmaceutical composition comprising the composition of claim 2 and a pharmaceutically acceptable excipient.
16. A polynucleotide encoding the composition of claim 2.
17. A pharmaceutical composition comprising the polynucleotide of claim 16 and a pharmaceutically acceptable excipient.

18. A vector comprising a polynucleotide of claim 16.
19. A cell comprising the polynucleotide of claim 16.
20. The cell of claim 19, wherein said cell is an immune cell for adoptive cell transfer (ACT), and optionally wherein the immune cell is a CD8⁺ T cell, a CD4⁺ T cell, a memory T cell, a terminally differentiated effector T cell, a natural killer (NK) cell, a NK T cell, a tumor infiltrating lymphocyte (TIL), a cytotoxic T lymphocyte (CTL), a regulatory T cell (Treg), or a dendritic cell (DC).
21. A pharmaceutical composition comprising the cell of claim 19 and a pharmaceutically acceptable excipient.
22. A method of producing a modified cell, said method comprising introducing into a cell a nucleic acid molecule comprising the polynucleotide of claim 16.
23. A method of modulating expression, function, and/or level of a payload in the cell of claim 19, said method comprising:
administering to the cell a stimulus,
wherein the SRE is responsive to the stimulus and wherein the expression, function, and/or level of the payload is modulated in response to the stimulus.
24. A method of inducing an immune response in the immune cell of claim 20, wherein the payload is an immunotherapeutic agent, said method comprising:
administering to the cell a therapeutically effective amount of a stimulus to modulate the expression of the immunotherapeutic agent, wherein the immunotherapeutic agent is capable of inducing an immune response in the cell in response to the stimulus.
25. A cell of claim 20 for use in a method of reducing a tumor burden in a subject, comprising:
(a) administering to the subject a therapeutically effective amount of the cells; and
(b) administering to the subject, a therapeutically effective amount of a stimulus,
wherein the stimulus is a ligand, to modulate the expression of the immunotherapeutic agent, thereby reducing the tumor burden.

26. A cell of claim 19 for use in a method of treating a disease in a subject in need thereof, said method comprising:

- (a) administering to the subject a therapeutically effective amount of the cell, wherein the cell comprises a payload that treats the disease; and
- (b) administering to the subject a therapeutically effective amount of a stimulus, wherein the SRE is responsive to the stimulus and wherein expression of the payload is modulated in response to the stimulus to thereby treat the disease.