

CLAIMS

1. A nucleic acid molecule comprising a polynucleotide encoding a recombinant protein comprising a drug responsive domain (DRD) operably linked to an IL15 payload, wherein said DRD is derived from human carbonic anhydrase II (CA2) and comprises the amino acid sequence of SEQ ID NO:4 and said IL15 payload is a membrane-bound IL15 polypeptide, and wherein said IL15 payload further comprises an intracellular tail derived from B7-1 comprising the amino acid sequence of SEQ ID NO:18.
2. The nucleic acid molecule of claim 1, wherein the DRD consists of the amino acid sequence of SEQ ID NO:4.
3. The nucleic acid molecule of claim 1, wherein the membrane-bound IL15 polypeptide comprises the amino acid sequence of SEQ ID NO:8.
4. The nucleic acid molecule of claim 3, wherein the membrane-bound IL15 polypeptide is N-terminal to the DRD.
5. The nucleic acid molecule of claim 4, wherein the membrane-bound IL15 polypeptide comprises an IL15 polypeptide component comprising the amino acid sequence of SEQ ID NO:8, a transmembrane domain and B7-1 intracellular tail comprising the amino acid sequence of SEQ ID NO:18, wherein the transmembrane domain is C-terminal to the IL15 polypeptide component and the intracellular tail is C-terminal to the transmembrane domain.
6. The nucleic acid molecule of claim 5, wherein the membrane-bound IL15 polypeptide further comprises a linker between the IL15 polypeptide component and the transmembrane domain and a leader sequence N-terminal to the IL15 polypeptide component.
7. The nucleic acid molecule of claim 6, wherein the polynucleotide encodes the amino acid sequence of SEQ ID NO:28.
8. The nucleic acid molecule of claim 7, wherein the polynucleotide comprises the nucleic acid

sequence of SEQ ID NO:29.

9. A vector comprising the nucleic acid molecule of claim 7.
10. The vector of claim 9, wherein the vector is a plasmid or a viral vector.
11. The vector of claim 10, wherein the viral vector is selected from a lentiviral vector, adenoviral vector, AAV vector, herpes simplex viral vector, retroviral vector or oncolytic viral vector.
12. The vector of claim 11, wherein the viral vector is a lentiviral vector.
13. A method of producing a genetically engineered T cell, natural killer (NK) cell or tumor infiltrating lymphocyte (TIL), comprising transducing the T cell, NK cell or TIL with the lentiviral vector of claim 12.
14. An isolated cell comprising the vector of claim 9.
15. An isolated cell comprising the nucleic acid molecule of claim 7.
16. The isolated cell of claim 15, wherein the cell is a mammalian cell.
17. The isolated cell of claim 16, wherein the mammalian cell is a human cell.
18. The isolated cell of claim 17, wherein the human cell is a T cell, natural killer (NK) cell, or tumor infiltrating lymphocyte (TIL).
19. A pharmaceutical composition comprising the cell of claim 18, and a pharmaceutically acceptable carrier.
20. A method of modulating the expression, function, and/or level of IL15 in the cell of claim 18, said method comprising administering acetazolamide to the cell, wherein the acetazolamide is administered in an amount sufficient to modulate the expression, function and/or level of IL15.
21. A recombinant protein encoded by the nucleic acid molecule of claim 7.