CLAIMS

What is claimed is:

1. A recombinant nucleic acid vector, comprising:

   a viral genome comprising a recombinant sequence portion encoding a plurality of genes, wherein the recombinant sequence portion is operably coupled to a regulatory sequence to allow for expression of the plurality of genes; and

   wherein the plurality of genes encode four distinct stimulatory molecules and an inhibitory ligand for an immune checkpoint receptor; and

   wherein the viral genome has at least one mutated or deleted protein coding sequence to reduce immunogenicity of a virus encoded by the viral genome.

2. The recombinant nucleic acid vector of claim 1 wherein at least one of the four distinct stimulatory molecules is selected form the group consisting of CD80 (B7.1), CD86 (B7.2), CD54 (ICAM-1/BB2), and CD11 (LFA-1).

3. The recombinant nucleic acid vector of claim 1 wherein at least two of the four distinct stimulatory molecules is selected form the group consisting of CD80 (B7.1), CD86 (B7.2), CD54 (ICAM-1/BB2), and CD11 (LFA-1).

4. The recombinant nucleic acid vector of claim 1 wherein at least three of the four distinct stimulatory molecules is selected form the group consisting of CD80 (B7.1), CD86 (B7.2), CD54 (ICAM-1/BB2), and CD11 (LFA-1).

5. The recombinant nucleic acid vector of claim 1 wherein the four distinct stimulatory molecules are CD80 (B7.1), CD86 (B7.2), CD54 (ICAM-1/BB2), and CD11 (LFA-1).

6. The recombinant nucleic acid vector of any one of the preceding claims wherein the immune checkpoint receptor is CTLA-4 or PD-1, and optionally wherein the inhibitory ligand comprises a transmembrane domain that anchors the ligand to a cell membrane.

7. The recombinant nucleic acid vector of any one of the preceding claims wherein the recombinant sequence portion further comprises a human cancer-associated sequence.

8. The recombinant nucleic acid vector of claim 7 wherein the human cancer-associated sequence further comprises a trafficking sequence that preferentially directs a gene

product encoded by the cancer-associated sequence to a cytoplasmic compartment of a cell hosting the recombinant nucleic acid vector.

9. The recombinant nucleic acid vector of claim 7 wherein the human cancer-associated sequence further comprises a trafficking sequence that preferentially directs a gene product encoded by the cancer-associated sequence to a lysosomal or endosomal compartment of a cell hosting the recombinant nucleic acid vector.

10. The recombinant nucleic acid vector of claim 7 wherein the human cancer-associated sequence encodes a protein selected from the group consisting of a cancer associated antigen, a cancer specific antigen, and a patient- and tumor-specific neoantigen.

11. The recombinant nucleic acid vector of any one of the preceding claims wherein the virus is an adenovirus.

12. The recombinant nucleic acid vector of claim 11 wherein the at least one mutated or deleted protein coding sequence is selected from the group consisting of E1, E2b, and E3.

13. The recombinant nucleic acid vector of any one of the preceding claims wherein the virus is replication deficient.

14. The recombinant nucleic acid vector of claim 1 wherein the immune checkpoint receptor is CTLA-4 or PD-1, and optionally wherein the inhibitory ligand comprises a transmembrane domain that anchors the ligand to a cell membrane.

15. The recombinant nucleic acid vector of claim 1 wherein the recombinant sequence portion further comprises a human cancer-associated sequence.

16. The recombinant nucleic acid vector of claim 15 wherein the human cancer-associated sequence further comprises a trafficking sequence that preferentially directs a gene product encoded by the cancer-associated sequence to a cytoplasmic compartment of a cell hosting the recombinant nucleic acid vector.

17. The recombinant nucleic acid vector of claim 15 wherein the human cancer-associated sequence further comprises a trafficking sequence that preferentially directs a gene product encoded by the cancer-associated sequence to a lysosomal or endosomal compartment of a cell hosting the recombinant nucleic acid vector.

18. The recombinant nucleic acid vector of claim 15 wherein the human cancer-associated sequence encodes a protein selected from the group consisting of a cancer associated antigen, a cancer specific antigen, and a patient- and tumor-specific neoantigen.

19. The recombinant nucleic acid vector of claim 1 wherein the virus is an adenovirus.

20. The recombinant nucleic acid vector of claim 19 wherein the at least one mutated or deleted protein coding sequence is selected from the group consisting of E1, E2b, and E3.

21. The recombinant nucleic acid vector of claim 1 wherein the virus is replication deficient.

22. A virus comprising the recombinant nucleic acid vector of any one of claims 1-13.

23. The virus of claim 22 wherein the virus is a recombination deficient adenovirus lacking the E2b gene.

24. The virus of claim 23 wherein the four distinct stimulatory molecules are CD80 (B7.1), CD86 (B7.2), CD54 (ICAM-1/BB2), and CD11 (LFA-1), wherein the immune checkpoint receptor is CTLA-4, and wherein the recombinant sequence portion further comprises a human cancer-associated sequence.

25. A virus comprising the recombinant nucleic acid vector of any one of claims 14-21.

26. The virus of claim 25 wherein the virus is a recombination deficient adenovirus lacking E2b gene.

27. The virus of claim 26 wherein the four distinct stimulatory molecules are CD80 (B7.1), CD86 (B7.2), CD54 (ICAM-1/BB2), and CD11 (LFA-1), wherein the immune checkpoint receptor is CTLA-4, and wherein the recombinant sequence portion further comprises a human cancer-associated sequence.

28. Use of a virus according to any one of claims 22-24 to infect an antigen presenting cell to thereby stimulate T cell activation in a T cell that contacts the antigen presenting cell.

29. The use of claim 28 wherein the antigen presenting cell is infected in a cutaneous layer.

30. A method of stimulating an immune response in a mammal in need thereof, comprising a step of administering a virus according to any one of claims 22-24 under a protocol effective to stimulate the immune response.

31. The method of claim 30 wherein the step of administering is performed by subcutaneous or subdermal injection.

32. The method of claim 30 further comprising administering a low-dose chemotherapy or a low-dose radiation therapy to the mammal.

33. The method of claim 32 wherein the low-dose chemotherapy or the low-dose radiation therapy is metronomically administered.