CLAIMS

1. A ribonucleic acid comprising two non-natural pre-miRNA sequences, wherein each pre-miRNA sequence comprises a guide miRNA that inhibits the expression of an immune checkpoint protein.

2. The ribonucleic acid of claim 1, wherein the two non-natural pre-miRNA sequences are separated from each other by at least 10 nucleotides.

3. The ribonucleic acid of claim 1, wherein each non-natural pre-miRNA sequence targets a different gene or different regions of the same gene.

4. The ribonucleic acid of claim 1, wherein each non-natural pre-miRNA comprises backbone sequences that are identical to the corresponding backbone sequences of a naturally-occurring pre-miRNA.

5. The ribonucleic acid of claim 1, wherein each non-natural pre-miRNA comprises backbone sequences from miR16, miR17, miR19, miR21, miR22, miR26a1, miR29b1, miR30a, miR122, miR126, miR133a1, miR142, miR150, miR155, miR204, miR206, miR214, miR412, miR486, miR494, or miR1915.

6. The ribonucleic acid of claim 1, wherein each non-natural pre-miRNA comprises backbone sequences from miR204 or miR206.

7. The ribonucleic acid of claim 1, wherein the immune checkpoint protein is CTLA4, CD70, PD-1, PD-L1, TIGIT, TIM3, LAG3, GITR, or PIK3IP1.

8. The ribonucleic acid of claim 1, wherein the immune checkpoint protein is PD-1.

9. A deoxyribonucleic acid encoding the ribonucleic acid of any one of claims 1–8.

10. The deoxyribonucleic acid of claim 9, further encoding a protein.

11. The deoxyribonucleic acid of claim 10, wherein the protein is a chimeric antigen receptor.

12. The deoxyribonucleic acid of claim 11, wherein the chimeric antigen receptor comprises an antigen-binding domain that binds CD19, CD22, CD33, MUC-16, or ROR-1.

13. The deoxyribonucleic acid of claim 11, further encoding: (a) a fusion protein comprising: (i) IL-15, or a functional fragment or variant thereof, and (ii) IL-15Rα, or a functional fragment or variant thereof; and (b) a cell tag.

14. A vector comprising the ribonucleic acid of any one of claims 1–8 or the deoxyribonucleic acid of any one of claims 9–13.

15. The vector of claim 14, wherein the vector is a *Sleeping Beauty* transposon.

16. The vector of claim 14, wherein the vector is an adenoviral vector.

17. A method for modifying the expression of a gene in a cell, wherein the method comprises introducing the ribonucleic acid of any one of claims 1–8 or the deoxyribonucleic acid of any one of claims 9–13 to the cell.

18. A genetically-modified cell comprising the ribonucleic acid of any one of claims 1–8 or the deoxyribonucleic acid of any one of claims 9–13.

19. A composition comprising: (a) the ribonucleic acid of any one of claims 1–8; (b) the deoxyribonucleic acid of any one of claims 9–13; or (c) the cell of claim 18.

20. The composition of claim 19 for use in the treatment of a disease or disorder in a subject.