Claims

We claim:

1. An engineered nucleic acid whose nucleotide sequence includes a sequence element that is or is a complement of an oncoselective translation sequence element.

2. The engineered nucleic acid of claim 1, wherein the engineered nucleic acid's nucleotide sequence includes an open reading frame or complement thereof.

3. The engineered nucleic acid of claim 2, wherein the oncoselective translation sequence element is or comprises an oncoselective read-through motif within or upstream of the open reading frame.

4. The engineered nucleic acid of claim 3 wherein the oncoselective readthrough motif comprises an upstream flanking sequence, a stop codon, and a downstream flanking sequence.

5. The engineered nucleic acid of any of the preceding claims , wherein an oncoselective readthrough motif comprises a sequence selected from the group comprising: VNNNNNNMNNMWK, NNNVWNNKGHHNH, DVHVNNNCWNNNB, MWBNNNNNNNNNN, WGNNSNHNHDNNN, VNNNNNNMNNMWK or VMNNWNKNNNNNN, wherein V stands for A, C or G, M stands for A or C, W stands for A or T/U, K stands for G or T/U, H stands for A, C or T/U, D stands for A,G or T/U, B stands for C, G or T/U, S stands for G or C, N stands for any nucleotide, within the region that spans the readthrough stop codon and the first 14 nucleotides of the downstream flanking sequence.

6. The engineered nucleic acid of any of the preceding claims, wherein the oncoselective read through motif comprises a stem loop; a bulge loop, a pseudoknot, or a combination thereof within the first 50 nucleotides of the downstream flanking sequence and part of this stem loop located preferably within stop codon and the first 16 nucleotides of the downstream flanking sequence, or a combination thereof.

7. The engineered nucleic acid of any of the preceding claims, wherein a stem loop comprises more than 20 base paired nucleotides within first 50 nucleotides of the downstream flanking sequence.

8. The engineered nucleic acid of any of the preceding claims, wherein an oncoselective read through motif comprises a downstream flanking sequence with a GC content of more than 42%, more than 48%, preferably more than 54%.

9. The engineered nucleic acid of any of the preceding claims, wherein an oncoselective read through motif comprises a codon that encodes proline residue.

10. The engineered nucleic acid of any of the preceding claims, wherein the open reading frame encodes a suicide protein.

11. The engineered nucleic acid of claim 10, wherein the suicide protein induces necroptosis.

12. The engineered nucleic acid of claim 11, wherein the suicide protein is constitutively active MLKL.

13. The engineered nucleic acid of claim 10, wherein the suicide protein induces pyroptosis.

14. The engineered nucleic acid of claim 13, wherein the suicide protein is constitutively active gasdermin D.

15. The engineered nucleic acid of claim 1, wherein the engineered nucleic acid has reduced immunogenicity.

16. A nucleic acid whose sequence includes an open reading frame, or a complement thereof, into or before which an oncoselective read-through motif has been engineered, wherein the open reading frame encodes a payload protein selected from the group consisting of a suicide protein, cell surface antigen, an antibody agent, a toxin, a genetic modification protein, or a viral replication protein.

17. A pharmaceutical composition comprising the nucleic acid of claim 1.

18. The pharmaceutical composition of claim 17, wherein the pharmaceutical composition comprises nanoparticles.

19. The pharmaceutical composition of claim 18, wherein the nanoparticles are lipid nanoparticles

20. The pharmaceutical composition of claim 18, wherein the engineered nucleic acid is or comprises RNA

21. The pharmaceutical composition of claim 18, wherein the engineered nucleic acid is or comprises DNA

22. The pharmaceutical composition of claim 18, wherein the engineered nucleic acid is expressed in a cell so that administration of the pharmaceutical composition delivers RNA to the cell.

23. ~~A method of treating cancer in a subject, wherein the method comprises administering a therapeutically effective amount of the~~The engineered nucleic acid of claim 1 or the pharmaceutical composition of claim 17 for use in therapy.

24. Use of the engineered nucleic acid of claim 1 or the pharmaceutical composition of claim 17 in the manufacture of a medicament for the treatment of cancer in a subject, wherein the engineered nucleic acid or the pharmaceutical composition is to be administered to the subject.

25~~24~~. ~~The method of claim 23~~The use according to claim 24, wherein the cancer in the subject comprises oncogenic ribosomes.

26~~25~~. ~~The method of claim 24~~The use according to claim 25, wherein the oncogenic ribosomes comprises at least one of loss of p53 activity, loss of RB activity, FBL overexpression, or hemizygous loss of ribosomal protein genes.

27~~26~~. ~~The method of claim 23~~The use according to claim 24, wherein ~~the subject is not recieving~~ aminoglycoside antibiotics, macrolide antibiotics, ataluren, or ivacaftor, ivacaftor/lumacaftor is not received by the subject.

28~~27~~. ~~The method of claim 23~~The use according to claim 24, wherein the subject is not suffering from Diamond–Blackfan anemia, Dyskeratosis congenita, Shwachman–Diamond syndrome, 5q-myelodysplastic syndrome, Treacher Collins syndrome, Cartilage–hair hypoplasia, Isolated congenital asplenia, Bowen–Conradi syndrome, or North American Indian childhood cirrhosis.

29~~28~~. ~~The method of claim 23~~The use according to claim 24, wherein the subject is to be administered ~~step of administering comprises administering~~ a plurality of doses.

30~~29~~. ~~The method of claim 23~~The use according to claim 24, wherein ~~further comprising a step of monitoring~~ one or more features of an immune response to the cancer is to be monitored in the subject.

31~~30~~. ~~The method of claim 29~~The use according to claim 30, wherein ~~the step of administering comprises continuing to administer~~ further doses are to be administered until

~~the monitoring detects~~ the immune response is ~~established~~detected from monitoring the subject.

32~~31~~. An oncoselective translation sequence element comprising a read-through consensus sequence, sequence with high G-C content; a codon encoding proline; a stem loop; a bulge loop, a pseudoknot or a combination thereof.

33~~32~~. A method of identifying an onco-selective nucleic acid sequences the method comprising transcriptome-wide translatome analysis.

34~~33~~. The method of claim 33~~32~~, wherein the method comprises Ribo-seq and LC/MS-based proteomics pipelines.