CLAIMS

WHAT IS CLAIMED IS:

1. A non-naturally occurring nucleic acid comprising a sequence encoding a biologic comprising an anti-angiogenic agent, said sequence comprising a modification in a coding region of the sequence as compared to an otherwise comparable sequence lacking the modification in the coding region, said modification comprising a replacement of at least four non-AGG arginine codons with AGG.

2. The non-naturally occurring nucleic acid of claim 1, wherein the sequence that encodes the anti-angiogenic agent further comprises a second modification.

3. The non-naturally occurring nucleic acid of claim 2, wherein the second modification is in at least one codon of the coding region of the sequence, and wherein the second modification is selected from the group consisting of:

(a) replacement of at least one non-CCC proline codon with CCC;

(b) replacement of at least one non-TCC serine codon with TCC;

(c) replacement of at least one non-CCG proline codon with CCG; and

(d) any combination of (a)-(c).

4. The non-naturally occurring nucleic acid of claim 3, wherein the at least one non-CCC proline codon of (a) is CCT; the at least one non-TCC serine codon of (b) is AGC; the at least one non-CCG proline codon of (c) is CCC, or any combination thereof.

5. The non-naturally occurring nucleic acid of any one of claims 1-4, wherein the anti-angiogenic agent is selected from the group consisting of: a VEGF inhibitor, a multi-tyrosine kinase inhibitor, a receptor tyrosine kinase inhibitor, an inhibitor of Akt phosphorylation, a PDGF-1 inhibitor, a PDGF-2 inhibitor, a NP-1 inhibitor, a NP-2 inhibitor, a Del 1 inhibitor, and an integrin inhibitor.

6. The non-naturally occurring nucleic acid of claim 5, wherein the anti-angiogenic agent comprises the VEGF inhibitor, and wherein the VEGF inhibitor is a non-antibody inhibitor.

7. The non-naturally occurring nucleic acid of claim 6, wherein the non-antibody inhibitor is a fusion protein that comprises human VEGF receptors 1 and 2.

8. The non-naturally occurring nucleic acid of claim 7, wherein the fusion protein comprises VEGF-Trap or a modified version thereof.

9. The non-naturally occurring nucleic acid of any one of claims 1-8, wherein the non-naturally occurring nucleic acid further comprises a signal peptide.

10. The non-naturally occurring nucleic acid of claim 9, wherein the signal peptide is selected from the group consisting of: human antibody heavy chain (Vh), human antibody light chain (Vl), and VEGF-Trap.

11. The non-naturally occurring nucleic acid of any one of claims 1-10, wherein the non-naturally occurring nucleic acid further comprises an intronic sequence.
12. The non-naturally occurring nucleic acid of claim 11, wherein the intronic sequence is selected from the group consisting of: hCMV intron A, adenovirus tripartite leader sequence intron, SV40 intron, hamster EF-1 alpha gene intron 1, intervening sequence intron, human growth hormone intron, and human beta globin intron.
13. The non-naturally occurring nucleic acid of any one of claims 1-12, wherein the non-naturally occurring nucleic acid further comprises a promoter.
14. The non-naturally occurring nucleic acid of claim 13, wherein the promoter is selected from the group consisting of: a cytomegalovirus (CMV) promoter, an elongation factor 1 alpha (EF1α) promoter, a simian vacuolating virus (SV40) promoter, a phosphoglycerate kinase (PGK1) promoter, a ubiquitin C (Ubc) promoter, a human beta actin promoter, a CAG promoter, a Tetracycline response element (TRE) promoter, a UAS promoter, an Actin 5c (Ac5) promoter, a polyhedron promoter, a Ca2+/calmodulin-dependent protein kinase II (CaMKIIa) promoter, a GAL1 promoter, a GAL 10 promoter, a TEF1 promoter, a glyceraldehyde 3-phosphage dehydrogenase (GDS) promoter, an ADH1 promoter, a CaMV35S promoter, a Ubi promoter, a human polymerase III RNA (H1) promoter, a U6 promoter, a polyadenylated construct thereof, and any combination thereof.
15. The isolated, non-naturally occurring nucleic acid of claim 14, wherein the promoter is the CMV promoter.
16. The non-naturally occurring nucleic acid of any one of claims 1-15, wherein the non-AGG arginine codon is AGA.
17. The non-naturally occurring nucleic acid of any one of claims 1-16, wherein the nucleic acid comprises a viral vector sequence.
18. The non-naturally occurring nucleic acid of claim 17, wherein the viral vector sequence comprises an AAV vector comprising a serotype AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, or any combination thereof.
19. The non-naturally occurring nucleic acid of any one of claims 1-18, wherein the non-naturally occurring nucleic acid comprises at least about 60% sequence identity or similarity with any one of **SEQ ID NOS: 13-19, 21-27, 31, 62, 64, 66,** or **68**.
20. A biologic encoded by the non-naturally occurring nucleic acid of any one of claims 1-19.
21. The biologic of claim 20, wherein the biologic comprises at least about 60%, about 70%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or up to about 100% sequence identity with **SEQ ID NO: 12**.

22. An engineered cell comprising the non-naturally occurring nucleic acid of any one of claims 1-19.

23. A plurality of adeno-associated viral (AAV) particles comprising the non-naturally occurring nucleic acid of any one of claims 1-19.

24. A composition comprising the plurality of AAV particles of claim 23 in unit dosage form.

25. A container comprising: (a) the non-naturally occurring nucleic acid of any one of claims 1-19; (b) the biologic of claim 20 or 21; (c) the engineered cell of claim 22, or (d) the plurality of AAV particles of claim 23.

26. A method of modifying cells, the method comprising contacting:

(a) a plurality of cells with the non-naturally occurring nucleic acid of any one of claims 1-19;

(b) a plurality of cells with the plurality of adeno-associated viral (AAV) particles of claim 23; or

(c) both (a) and (b).

27. A pharmaceutical composition comprising: (a) the non-naturally occurring nucleic acid of any one of claims 1-19; (b) the biologic of claim 20 or 21; or (c) the plurality of AAV particles of claim 23.

28. The (a) non-naturally occurring nucleic acid of any one of claims 1-19; (b) biologic of claim 20 or 21; (c) plurality of AAV particles of claim 23; or (d) pharmaceutical composition of claim 27, for use as a medicament.