Claims

1. An artificial nucleic acid molecule comprising:

   a. at least one 5'-untranslated region element (5'UTR element) which comprises or consists of

      a nucleic acid sequence which has an identity of at least 95% to a nucleic acid sequence according to SEQ ID NOs. 1368, 1452, 1453, 1454, 1455, 1456, 1457 or 1458, or a corresponding RNA sequence,

      or

      a functional fragment of a nucleic acid sequence, which has an identity of at least 95% to a nucleic acid sequence according to SEQ ID NOs. 1368, 1452, 1453, 1454, 1455, 1456, 1457 or 1458, or a corresponding RNA sequence; and

   b. at least one open reading frame (ORF),

      and wherein the 5'UTR element is suitable for increasing protein production from the artificial nucleic acid molecule.

2. The artificial nucleic acid molecule according to claim 1, further comprising:

   c. at least one histone stem-loop.

3. The artificial nucleic acid molecule according to claim 1 or 2, wherein the 5'UTR element and the open reading frame are heterologous.

4. The artificial nucleic acid molecule according to any one of claims 1-3, wherein the 5'UTR element does not comprise a TOP-motif, preferably wherein the nucleic acid sequence having an identity of at least 95% to a nucleic acid sequence according to SEQ ID NOs. 1368, 1452, 1453, 1454, 1455, 1456, 1457 or 1458, or a corresponding

RNA sequence, preferably the 5'UTR element, starts at its 5'-end with a nucleotide located at position 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 downstream of the polypyrimidine tract.

5. The artificial nucleic acid molecule according to any one of claims 1-4, wherein the nucleic acid sequence having an identity of at least 95% to a nucleic acid sequence according to SEQ ID NOs. 1368, 1452, 1453, 1454, 1455, 1456, 1457 or 1458, or a corresponding RNA sequence, preferably the 5'UTR element, terminates at its 3'-end with a nucleotide located at position 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 upstream of the start codon of the gene it is derived from.

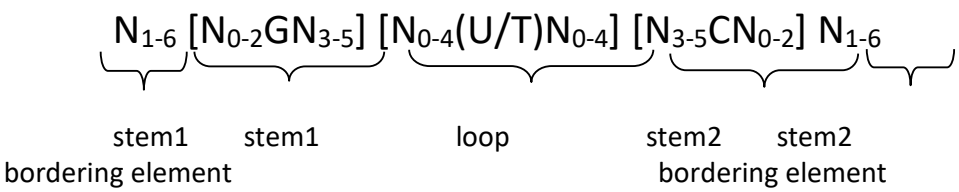
6. The artificial nucleic acid molecule according to any one of claims 1-5, wherein the 5'UTR element does not comprise a start codon or an open reading frame.

7. The artificial nucleic acid molecule according to any one of claims 2-6, wherein the at least one histone stem-loop is selected from following formulae (I) or (II):

formula (I) (stem-loop sequence without stem bordering elements):

$$\underbrace{[N_{0-2}GN_{3-5}]}_{\text{stem1}}\ \underbrace{[N_{0-4}(U/T)N_{0-4}]}_{\text{loop}}\ \underbrace{[N_{3-5}CN_{0-2}]}_{\text{stem2}}$$

formula (II) (stem-loop sequence with stem bordering elements):



wherein:

stem1 or stem2 bordering elements N_{1-6} is a consecutive sequence of 1 to 6, preferably of 2 to 6, more preferably of 2 to 5, even more preferably of 3 to 5, most preferably of 4 to 5 or 5 N, wherein each N is independently from another selected from a nucleotide selected from A, U, T, G and C, or a nucleotide analogue thereof;

stem1 $[N_{0-2}GN_{3-5}]$ is reverse complementary or partially reverse complementary with element stem2, and is a consecutive sequence between of 5 to 7 nucleotides;

wherein N_{0-2} is a consecutive sequence of 0 to 2, preferably of 0 to 1, more preferably of 1 N, wherein each N is independently from another selected from a nucleotide selected from A, U, T, G and C or a nucleotide analogue thereof;

wherein N_{3-5} is a consecutive sequence of 3 to 5, preferably of 4 to 5, more preferably of 4 N, wherein each N is independently from another selected from a nucleotide selected from A, U, T, G and C or a nucleotide analogue thereof, and

wherein G is guanosine or an analogue thereof, and may be optionally replaced by a cytidine or an analogue thereof, provided that its complementary nucleotide cytidine in stem2 is replaced by guanosine;

loop sequence [N_{0-4}(U/T)N_{0-4}] is located between elements stem1 and stem2, and is a consecutive sequence of 3 to 5 nucleotides, more preferably of 4 nucleotides;

wherein each N_{0-4} is independent from another a consecutive sequence of 0 to 4, preferably of 1 to 3, more preferably of 1 to 2 N, wherein each N is independently from another selected from a nucleotide selected from A, U, T, G and C or a nucleotide analogue thereof; and

wherein U/T represents uridine, or optionally thymidine;

stem2 [$N_{3-5}CN_{0-2}$] is reverse complementary or partially reverse complementary with element stem1, and is a consecutive sequence between of 5 to 7 nucleotides;

wherein N_{3-5} is a consecutive sequence of 3 to 5, preferably of 4 to 5, more preferably of 4 N, wherein each N is independently from another selected from a nucleotide selected from A, U, T, G and C or a nucleotide analogue thereof;

wherein N_{0-2} is a consecutive sequence of 0 to 2, preferably of 0 to 1, more preferably of 1 N, wherein each N is independently from another selected from a nucleotide selected from A, U, T, G and C or a nucleotide analogue thereof; and

wherein C is cytidine or an analogue thereof, and may be optionally replaced by a guanosine or an analogue thereof provided that its complementary nucleotide guanosine in stem1 is replaced by cytidine;

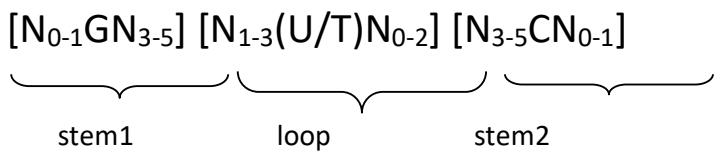
wherein

stem1 and stem2 are capable of base pairing with each other

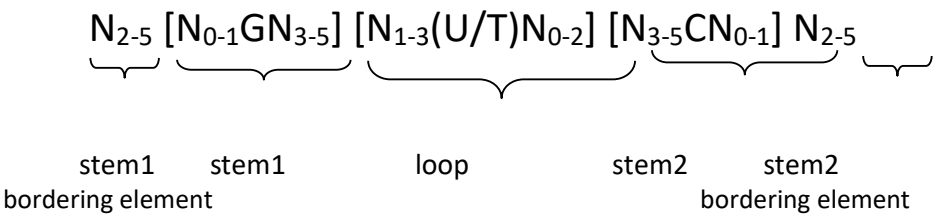
forming a reverse complementary sequence, wherein base pairing may occur between stem1 and stem2, or

forming a partially reverse complementary sequence, wherein an incomplete base pairing may occur between stem1 and stem2.

8. The artificial nucleic acid molecule according to any one of claims 2-7, wherein the at least one histone stem-loop is selected from at least one of following formulae (Ia) or (IIa):



formula (Ia) (stem-loop sequence without stem bordering elements)



formula (IIa) (stem-loop sequence with stem bordering elements)

9. The artificial nucleic acid molecule according to any one of claims 1-8, further comprising

d. a poly(A) sequence and/or a polyadenylation signal.

10. The artificial nucleic acid molecule according to any of claims 1-9, further comprising:

e. a poly(C) sequence.

11. The artificial nucleic acid molecule according to any one of claims 1-10, further comprising:

f. at least one 3'UTR element.

12. The artificial nucleic acid molecule according to claim 11, wherein the at least one 3'UTR element comprises or consists of a nucleic acid sequence corresponding to a 3'UTR of a gene providing a stable mRNA or to a functional variant of the 3'UTR of a gene providing a stable mRNA, or to a functional fragment of said 3'UTR or of said functional variant.

13. The artificial nucleic acid molecule according to any one of claims 2-12, wherein the at least one histone stem-loop comprises or consists of a nucleic acid sequence selected from the group consisting of SEQ ID NOs. 1391-1433, preferably from the group consisting of SEQ ID NOs. 1403-1433.

14. The artificial nucleic acid molecule according to any one of claims 2-13, wherein the histone stem-loop comprises or consists of a nucleic acid sequence having a sequence identity of at least about 75%, preferably of at least about 80%, preferably of at least about 85%, more preferably of at least about 90%, even more preferably of at least about 95% to the sequence according to SEQ ID NO. 1433 or to the corresponding RNA sequence, wherein preferably positions 6, 13 and 20 of the sequence having a sequence identity of at least about 75%, preferably of at least about 80%, preferably at least about 85%, more preferably at least about 90%, even more preferably at least about 95% to the sequence according to SEQ ID NO. 1433 or to the corresponding RNA sequence are conserved, i.e. are identical to the nucleotides at positions 6, 13 and 20 of SEQ ID NO. 1433 or to the corresponding RNA nucleotides.

15. The artificial nucleic acid molecule according to any one of claims 11-14, wherein the 3'UTR element comprises or consists of a 3'UTR of a gene selected from the group consisting of an albumin gene, an α-globin gene, a β-globin gene, a tyrosine hydroxylase gene, a lipoxygenase gene, and a collagen alpha gene, or a functional variant of a 3'UTR of a gene selected from the group consisting of an albumin gene, an α-globin gene, a β-globin gene, a tyrosine hydroxylase gene, a lipoxygenase gene, and a collagen alpha gene, or a functional fragment of said 3'UTR or of said variant, wherein the at least one 3'UTR element preferably comprises or consists of

a nucleic acid sequence, which is derived from the 3'UTR of a vertebrate albumin gene or from a variant thereof, preferably from the 3'UTR of a mammalian albumin gene or from a variant thereof, more preferably from the 3'UTR of a human albumin gene or from a variant thereof, even more preferably from the 3'UTR of the human albumin gene according to GenBank Accession number NM_000477.5 or from a variant thereof; or

a nucleic acid sequence, which is derived from the 3'UTR of a vertebrate α-globin gene or from a variant thereof, preferably from the 3'UTR of a mammalian α-globin gene or from a variant thereof, more preferably from the 3'UTR of a human α-globin gene or from a variant thereof.

16. The artificial nucleic acid molecule according to any one of claims 11-15, wherein the at least one 3'UTR element comprises or consists of a nucleic acid sequence, which has an identity of at least about 95%, preferably of at least about 99%, to a nucleic acid sequence selected from SEQ ID NOs. 1369-1377 and 1434 or to a corresponding RNA sequence, or wherein the at least one 3'UTR element comprises or consists of a functional fragment of a nucleic acid sequence, which has an identity of at least about 95%, preferably of at least about 99%, to a nucleic acid sequence selected from SEQ ID NOs. 1369-1377 and 1434 or to a corresponding RNA sequence.

17. The artificial nucleic acid molecule according to any one of claims 1-16, wherein the artificial nucleic acid molecule, preferably the open reading frame, is at least partially G/C modified, preferably wherein the G/C content of the open reading frame is increased compared to the wild type open reading frame.

18. The artificial nucleic acid molecule according to any one of claims 1-17, which is an RNA, preferably an mRNA molecule.

19. A vector comprising:

a. at least one 5'-untranslated region element (5'UTR element) which comprises or consists of

a nucleic acid sequence which has an identity of at least 95% to a nucleic acid sequence according to SEQ ID NOs. 1368, 1452, 1453, 1454, 1455, 1456, 1457 or 1458, or a corresponding RNA sequence,

or

a functional fragment of a nucleic acid sequence, which has an identity of at least 95% to a nucleic acid sequence according to SEQ ID NOs. 1368, 1452, 1453, 1454, 1455, 1456, 1457 or 1458, or a corresponding RNA sequence; and

b. at least one open reading frame (ORF) and/or at least one cloning site, and wherein the 5'UTR element is suitable for increasing protein production from the artificial nucleic acid molecule.

20. The vector according to claim 19, further comprising:

c. at least one histone-stem loop.

21. The vector according to claim 19 or 20, which is a DNA vector, preferably a plasmid vector, or a viral vector.

22. The vector according to any one of claims 19-21, which comprises or codes for an artificial nucleic acid molecule according to any one of claims 1-18.

23. A cell comprising the artificial nucleic acid molecule according to any one of claims 1-18 or the vector according to any one of claims 19-22, wherein the cell is preferably a mammalian cell, more preferably an isolated cell of a mammalian subject, most preferably of a human subject.

24. A pharmaceutical composition comprising the artificial nucleic acid molecule according to any one of claims 1-18, the vector according to any one of claims 19-22, or the cell

according to claim 23, optionally further comprising one or more pharmaceutically acceptable diluents and/or excipients and/or one or more adjuvants.

25. The artificial nucleic acid molecule according to any one of claims 1-18, the vector according to any one of claims 19-22, the cell according to claim 23, or the pharmaceutical composition according to claim 24 for use as a medicament, preferably for use as a vaccine or for use in gene therapy.

26. An in vitro method for increasing protein production from an artificial nucleic acid molecule, comprising the step of providing the artificial nucleic acid molecule with

i. at least one 5'-untranslated region element (5'UTR element) which comprises or consists of

a nucleic acid sequence which has an identity of at least 95% to a nucleic acid sequence according to SEQ ID NOs. 1368, 1452, 1453, 1454, 1455, 1456, 1457 or 1458, or a corresponding RNA sequence,

or

a functional fragment of a nucleic acid sequence, which has an identity of at least 95% to a nucleic acid sequence according to SEQ ID NOs. 1368, 1452, 1453, 1454, 1455, 1456, 1457 or 1458, or a corresponding RNA sequence;

ii. preferably at least one histone stem-loop; and

iii. optionally, a poly(A) sequence and/or a polyadenylation signal, and wherein the 5'UTR element is suitable for increasing protein production from the artificial nucleic acid molecule.

27. In vitro use of a 5'UTR element, which comprises or consists of

a nucleic acid sequence which has an identity of at least 95% to a nucleic acid sequence according to SEQ ID NOs. 1368, 1452, 1453, 1454, 1455, 1456, 1457 or 1458, or a corresponding RNA sequence,

or

a functional fragment of a nucleic acid sequence, which has an identity of at least 95% to a nucleic acid sequence according to SEQ ID NOs. 1368, 1452, 1453, 1454, 1455, 1456, 1457 or 1458, or a corresponding RNA sequence and

preferably further comprises at least one histone stem-loop

for increasing protein production from a nucleic acid molecule.

28. A kit or kit of parts comprising an artificial nucleic acid molecule according to any one of claims 1-18, the vector according to any one of claims 19-22, the cell according to claim 23, and/or the pharmaceutical composition according to claim 24, the kit or kit of parts preferably further comprising instructions for use, cells for transfection, an adjuvant, a means for administration of the pharmaceutical composition, a pharmaceutically acceptable carrier and/or a pharmaceutically acceptable solution for dissolution or dilution of the artificial nucleic acid molecule, the vector or the pharmaceutical composition.