Claims

1. An artificial nucleic acid molecule comprising

   a. at least one open reading frame (ORF); and

   b. at least one 3’-untranslated region element (3’-UTR element) heterologous to the ORF, wherein the at least one 3’-UTR element:

      prolongs and/or increases protein production from said artificial nucleic acid molecule; and

      comprises or consists of a nucleic acid sequence from the 3’-UTR of a transcript of GNAS (guanine nucleotide binding protein, alpha stimulating complex locus), wherein the 3' UTR element is selected from the group consisting of SEQ ID NO: 1, 2, 3, 4, 116, and a sequence having at least 90% sequence identity to SEQ ID NO: 1, 2, 3, 4, or 116.

2. The artificial nucleic acid molecule of claim 1, further comprising at least one 5’-untranslated region element (5’-UTR element), wherein the at least one 5’-UTR element prolongs and/or increases protein production from said artificial nucleic acid molecule and wherein the at least one 5’-UTR element additionally comprises a nucleic acid sequence from the the 5’-UTR of a transcript of a gene selected from the group consisting of NDUFA1 (NADH dehydrogenase (ubiquinone) 1 alpha subcomplex), MORN2 (MORN repeat containing 2), GSTM1 (glutathione S-transferase, mu 1), CBR2 (carbonyl reductase 2), MP68 (RIKEN cDNA 2010107E04 gene), NDUFA4 (NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 4), LTA4H, SLC38A6, DECR1, PIGK, FAM175A, PHYH, TBC1D19, PIGB, ALG6, CRYZ, BRP44L, ACADSB, SUPT3H, TMEM14A, GRAMD1C, C11orf80, C9orf46, ANXA4, TBCK, IFI6, C2orf34, ALDH6A1, AGTPBP1, CCDC53, LRRC28, CCDC109B, PUS10, CCDC104, CASP1, SNX14, SKAP2, NDUFB6, EFHA1, BCKDHB, BBS2, LMBRD1, ITGA6, HERC5, NT5DC1, RAB7A, AGA, TPK1, MBNL3, HADHB, MCCC2, CAT, ANAPC4, PCCB, PHKB, ABCB7, PGCP, GPD2, TMEM38B, NFU1, OMA1, LOC128322/NUTF2, NUBPL, LANCL1, HHLA3, PIR, ACAA2, CTBS, GSTM4, ALG8, Ndufa1, Atp5e, Gstm5, Uqcr11, Ifi27l2a, Cbr2, Anapc13, Atp5l, Tmsb10, Nenf, Ndufa7, Atp5k, 1110008P14Rik, Cox4i1, Cox6a1, Ndufs6, Sec61b, Romo1, Gnas, Snrpd2, Mgst3, Aldh2, Ssr4, Myl6, Prdx4, Ubl5, 1110001J03Rik, Ndufa13, Ndufa3,

Gstp2, Tmem160, Ergic3, Pgcp, Slpi, Myeov2, Ndufa4, Ndufs5, Gstm1, 1810027O10Rik, Atp5o, Shfm1, Tspo, S100a6, Taldo1, Bloc1s1, Hexa, Ndufb11, Map1lc3a, Morn2, Gpx4, Mif, Cox6b1, RIKEN cDNA2900010J23 (Swi5), Sec61g, 2900010M23Rik, Anapc5, Mars2, Phpt1, Ndufb8, Pfdn5, Arpc3, Ndufb7, Atp5h, Mrpl23, Uba52, Tomm6, Mtch1, Pcbd2, Ecm1, Hrsp12, Mecr, Uqcrq, Gstm3, Lsm4, Park7, Usmg5, Cox8a, Ly6c1, Cox7b, Ppib, Bag1, S100a4, Bcap31, Tecr, Rabac1, Robld3, Sod1, Nedd8, Higd2a, Trappc6a, Ldhb, Nme2, Snrpg, Ndufa2, Serf1, Oaz1, Rps4x, Rps13, Ybx1, Sepp1, Gaa, ACTR10, PIGF, MGST3, SCP2, HPRT1, ACSF2, VPS13A, CTH, NXT2, MGST2, C11orf67, PCCA, GLMN, DHRS1, PON2, NME7, ETFDH, ALG13, DDX60, DYNC2LI1, VPS8, ITFG1, CDK5, C1orf112, IFT52, CLYBL, FAM114A2, NUDT7, AKD1, MAGED2, HRSP12, STX8, ACAT1, IFT74, KIFAP3, CAPN1, COX11, GLT8D4, HACL1, IFT88, NDUFB3, ANO10, ARL6, LPCAT3, ABCD3, COPG2, MIPEP, LEPR, C2orf76, ABCA6, LY96, CROT, ENPP5, SERPINB7, TCP11L2, IRAK1BP1, CDKL2, GHR, KIAA1107, RPS6KA6, CLGN, TMEM45A, TBC1D8B, ACP6, RP6-213H19.1, SNRPN, GLRB, HERC6, CFH, GALC, PDE1A, GSTM5, CADPS2, AASS, TRIM6-TRIM34 (readthrough transcript), SEPP1, PDE5A, SATB1, CCPG1, CNTN1, LMBRD2, TLR3, BCAT1, TOM1L1, SLC35A1, GLYATL2, STAT4, GULP1, EHHADH, NBEAL1, KIAA1598, HFE, KIAA1324L, and MANSC1.

3. The artificial nucleic acid molecule according to claim 2, wherein each of the at least one open reading frame, the at least one 3’-UTR element and the at least one 5’-UTR element are heterologous to each other.

4. The artificial nucleic acid molecule of claim 1, further comprising at least one 5’-untranslated region element (5’-UTR element), wherein the at least one 5’-UTR element prolongs and/or increases protein production from said artificial nucleic acid molecule and wherein the at least one 5’-UTR element comprises or consists of a nucleic acid sequence from the 5’-UTR of a transcript of GNAS (guanine nucleotide binding protein, alpha stimulating complex locus).

5. The artificial nucleic acid molecule according to any of claims 1 to 4, wherein the at least one 3’-UTR element and/or the at least one 5’-UTR element are characterized by an mRNA decay wherein the ratio of the amount of said mRNA at a second point in time to the amount of said mRNA at a first point in time is at least 0.5 (50%), at least 0.6 (60%), at least 0.7 (70%), at least 0.75 (75%), at least 0.8 (80%), at least 0.85 (85%), at least 0.9 (90%), or at least 0.95 (95%).

6. The artificial nucleic acid molecule according to any of claims 1 to 5, wherein the artificial nucleic acid molecule does not comprise a 3'-UTR and/or a 5'-UTR of ribosomal protein S6, of RPL36AL, of rps16 or of ribosomal protein L9 and wherein the open reading frame of the artificial nucleic acid molecule does not code for a GFP protein and wherein the open reading frame of the artificial nucleic acid molecule does not code for a reporter protein.

7. The artificial nucleic acid molecule according to any of claims 1 to 6, wherein the at least one 3'-UTR element and/or the at least one 5'-UTR element prolongs protein production from said artificial nucleic acid molecule at least 1.2 fold, or at least 1.5 fold, more preferably at least 2 fold, or at least 2.5 fold, compared to the protein production from a reference nucleic acid molecule lacking a 3'-UTR and/or the at least one 5'-UTR, respectively, and/or wherein the at least one 3'-UTR element and/or the at least one 5'-UTR element increases protein production from said artificial nucleic acid molecule at least 1.5 fold, or at least 2 fold, or at least 2.5 fold, compared to the protein production from a reference nucleic acid molecule lacking a 3'-UTR and/or the at least one 5'-UTR, respectively.

8. The artificial nucleic acid molecule according to any one of claims 1 to 7 wherein the at least one 3'-UTR element additionally comprises a nucleic acid sequence which is derived from the 3'-UTR transcript of a gene selected from the group consisting of NDUFA1 (NADH dehydrogenase (ubiquinone) 1 alpha subcomplex), MORN2 (MORN repeat containing 2), GSTM1 (glutathione S-transferase, mu 1), CBR2 (carbonyl reductase 2), MP68 (RIKEN cDNA 2010107E04 gene), NDUFA4 (NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 4), LTA4H, SLC38A6, DECR1, PIGK, FAM175A, PHYH, TBC1D19, PIGB, ALG6, CRYZ, BRP44L, ACADSB, SUPT3H, TMEM14A, GRAMD1C, C11orf80, C9orf46, ANXA4, TBCK, IFI6, C2orf34, ALDH6A1, AGTPBP1, CCDC53, LRRC28, CCDC109B, PUS10, CCDC104, CASP1, SNX14, SKAP2, NDUFB6, EFHA1, BCKDHB, BBS2, LMBRD1, ITGA6, HERC5, NT5DC1, RAB7A, AGA, TPK1, MBNL3, HADHB, MCCC2, CAT, ANAPC4, PCCB, PHKB, ABCB7, PGCP, GPD2, TMEM38B, NFU1, OMA1, LOC128322/NUTF2, NUBPL, LANCL1, HHLA3, PIR, ACAA2, CTBS, GSTM4, ALG8, Ndufa1, Atp5e, Gstm5, Uqcr11, Ifi27l2a, Cbr2, Anapc13, Atp5l, Tmsb10, Nenf, Ndufa7, Atp5k, 1110008P14Rik, Cox4i1, Cox6a1, Ndufs6, Sec61b, Romo1, Gnas, Snrpd2, Mgst3, Aldh2, Ssr4, Myl6, Prdx4, Ubl5, 1110001J03Rik, Ndufa13, Ndufa3, Gstp2, Tmem160, Ergic3, Pgcp, Slpi, Myeov2, Ndufa4, Ndufs5, Gstm1, 1810027O10Rik, Atp5o, Shfm1, Tspo, S100a6, Taldo1, Bloc1s1, Hexa, Ndufb11, Map1lc3a, Morn2, Gpx4, Mif,

Cox6b1, RIKEN cDNA2900010J23 (Swi5), Sec61g, 2900010M23Rik, Anapc5, Mars2, Phpt1, Ndufb8, Pfdn5, Arpc3, Ndufb7, Atp5h, Mrpl23, Uba52, Tomm6, Mtch1, Pcbd2, Ecm1, Hrsp12, Mecr, Uqcrq, Gstm3, Lsm4, Park7, Usmg5, Cox8a, Ly6c1, Cox7b, Ppib, Bag1, S100a4, Bcap31, Tecr, Rabac1, Robld3, Sod1, Nedd8, Higd2a, Trappc6a, Ldhb, Nme2, Snrpg, Ndufa2, Serf1, Oaz1, Rps4x, Rps13, Ybx1, Sepp1, Gaa, ACTR10, PIGF, MGST3, SCP2, HPRT1, ACSF2, VPS13A, CTH, NXT2, MGST2, C11orf67, PCCA, GLMN, DHRS1, PON2, NME7, ETFDH, ALG13, DDX60, DYNC2LI1, VPS8, ITFG1, CDK5, C1orf112, IFT52, CLYBL, FAM114A2, NUDT7, AKD1, MAGED2, HRSP12, STX8, ACAT1, IFT74, KIFAP3, CAPN1, COX11, GLT8D4, HACL1, IFT88, NDUFB3, ANO10, ARL6, LPCAT3, ABCD3, COPG2, MIPEP, LEPR, C2orf76, ABCA6, LY96, CROT, ENPP5, SERPINB7, TCP11L2, IRAK1BP1, CDKL2, GHR, KIAA1107, RPS6KA6, CLGN, TMEM45A, TBC1D8B, ACP6, RP6-213H19.1, SNRPN, GLRB, HERC6, CFH, GALC, PDE1A, GSTM5, CADPS2, AASS, TRIM6-TRIM34 (readthrough transcript), SEPP1, PDE5A, SATB1, CCPG1, CNTN1, LMBRD2, TLR3, BCAT1, TOM1L1, SLC35A1, GLYATL2, STAT4, GULP1, EHHADH, NBEAL1, KIAA1598, HFE, KIAA1324L, and MANSC1;

9. The artificial nucleic acid molecule according to claim 8 wherein the at least one 3'-UTR element additionally comprises a nucleic acid sequence from the 3'-UTR transcript of a gene selected from the group consisting of NDUFA1 (NADH dehydrogenase (ubiquinone) 1 alpha subcomplex), GNAS (guanine nucleotide binding protein, alpha stimulating complex locus), MORN2 (MORN repeat containing 2), GSTM1 (glutathione S-transferase, mu 1), CBR2 (carbonyl reductase 2), MP68 (RIKEN cDNA 2010107E04 gene), NDUFA4 (NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 4), Ybx1 (Y-Box binding protein 1), Ndufb8 (NADH dehydrogenase (ubiquinone) 1 beta subcomplex 8), and CNTN1 (contactin 1).

10. The artificial nucleic acid molecule according to any one of claims 1 to 9 wherein the at least one 5'-UTR element comprises a nucleic acid sequence from the 5'-UTR of a transcript of a gene selected from the group consisting of NDUFA1 (NADH dehydrogenase (ubiquinone) 1 alpha subcomplex), GNAS (guanine nucleotide binding protein, alpha stimulating complex locus), MORN2 (MORN repeat containing 2), GSTM1 (glutathione S-transferase, mu 1), CBR2 (carbonyl reductase 2), MP68 (RIKEN cDNA 2010107E04 gene), NDUFA4 (NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 4), Ybx1 (Y-Box binding protein 1), Ndufb8 (NADH dehydrogenase (ubiquinone) 1 beta subcomplex 8), and CNTN1 (contactin 1) LTA4H, DECR1, PIGK, TBC1D19, BRP44L, ACADSB, SUPT3H, TMEM14A,

C9orf46, ANXA4, IFI6, C2orf34, ALDH6A1, CCDC53, CCDC104, CASP1, NDUFB6, BCKDHB, BBS2, HERC5, FAM175A, NT5DC1, RAB7A, AGA, TPK1, MBNL3, MCCC2, CAT, ANAPC4, PHKB, ABCB7, GPD2, TMEM38B, NFU1, LOC128322/NUTF2, NUBPL, LANCL1, PIR, CTBS, GSTM4, Ndufa1, Atp5e, Gstm5, Anapc13, Ndufa7, Atp5k, 1110008P14Rik, Cox4i1, Ndufs6, Sec61b, Snrpd2, Mgst3, Prdx4; Pgcp; Myeov2; Ndufa4; Ndufs5; Gstm1; Atp5o; Tspo; Taldo1; Bloc1s1; and Hexa.

11. The artificial nucleic acid molecule according to claim 10 wherein the at least one 5'-UTR element comprises or consists of a nucleic acid sequence which is derived from the 5'-UTR of a transcript of MP68 (RIKEN cDNA 2010107E04 gene) or NDUFA4 (NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 4).

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

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

13. The artificial nucleic acid molecule according to claim 12, wherein the poly(A) sequence or the polyadenylation signal is located 3' of the 3'-UTR element and/or wherein the polyadenylation signal comprises the consensus sequence NN(U/T)ANA, with N = A or U, AA(U/T)AAA or A(U/T)(U/T)AAA and/or wherein the polyadenylation signal, the consensus sequence NNUANA, is located less than about 50 nucleotides downstream of the 3'-end of the 3'-UTR element and/or wherein the poly(A) sequence has a length of about 20 to about 300 adenine nucleotides, or of about 40 to about 200 adenine nucleotides, or of about 50 to about 100 adenine nucleotides, or of about 60 to about 70 adenine nucleotides.

14. The artificial nucleic acid molecule according to any one of claims 1 to 13, further comprising a 5'-cap structure, a poly(C) sequence, a histone stem-loop, and/or an IRES-motif, wherein the histone stem-loop comprises a sequence according to SEQ ID NO: 34.

15. The artificial nucleic acid molecule according to any one of claims 1 to 14, wherein the nucleic acid comprises a 5'-TOP UTR and/or

    wherein the artificial nucleic acid molecule, the open reading frame, is at least partially G/C modified, wherein the G/C content of the open reading frame is increased compared to the wild type open reading frame and/or

wherein the open reading frame comprises a codon-optimized region, wherein the open reading frame is codon-optimized.

16. The artificial nucleic acid molecule according to claim 15 wherein the artificial nucleic acid molecule is an RNA or an mRNA molecule.

17. A vector comprising an artificial nucleic acid molecule according to any one of claims 1 to 16.

18. The vector according to claim 17 selected from the group consisting of a DNA vector, a plasmid vector, and a viral vector.

19. The vector according to claim 18, wherein the vetor is a plasmid vector.

20. A cell comprising the artificial nucleic acid molecule according to any one of claims 1 to 16 or the vector according to any one of claims 17 to 19.

21. The cell according to claim 20, wherein the cell is a mammalian cell.

22. A pharmaceutical composition comprising the artificial nucleic acid molecule according to any one of claims 1 to 16, the vector according to any one of claims 17 to 19, or the cell according to claim 20 or 21.

23. The pharmaceutical composition according to claim 22 further comprising one or more pharmaceutically acceptable vehicles, diluents, excipients, or adjuvants.

24. Use of the artificial nucleic acid molecule according to any one of claims 1 to 16, the vector according to any one of claims 17 to 19, the cell according to claim 20 or 21, or the pharmaceutical composition according to claim 22 or 23 for the manufacture of a medicament.

25. The use according to claim 24 wherein the medicament is for a vaccine or for gene therapy.

26. A method for increasing and/or prolonging protein production from an artificial nucleic acid molecule, from an mRNA molecule or a vector, the method comprising the step of associating an open reading frame with a 3'-UTR element and/or a 5'-UTR element, wherein the 3'-UTR element and/or the 5'-UTR element prolongs and/or increases protein production from a resulting artificial nucleic acid molecule and wherein the at least one 3'-UTR element and/or the at least one 5'-UTR element is from a stable mRNA, to obtain an artificial nucleic acid molecule, or an mRNA molecule, according to any of claims 1 to 16 or a vector according to any one of claims 17 to 19.

27. Use of a 3'-UTR element for increasing and/or prolonging protein production from an artificial nucleic acid molecule, from an mRNA molecule or a vector, wherein the 3'-UTR element comprises or consists of a nucleic acid sequence from the 3'-UTR of a transcript of GNAS (guanine nucleotide binding protein, alpha stimulating complex locus).

28. A kit comprising any one or more of an artificial nucleic acid molecule according to any one of claims 1 to 16, a vector according to any one of claims 17 to 19, a cell according to claim 20 or 21, and a pharmaceutical composition according to claim 22 or 23.

29. The kit according to claim 28 further comprising any one or more of instructions for use, cells for transfection, an adjuvant, a means for administration of the pharmaceutical composition, a pharmaceutically acceptable carrier, a pharmaceutically acceptable solution for dissolution or dilution of the artificial nucleic acid molecule, the vector, the cells, and the pharmaceutical composition.

30. The artificial nucleic acid molecule according to any one of claims 1 to 16, the vector according to any one of claims 17 to 19, the cell according to claim 20 or 21, or the pharmaceutical composition according to claim 22 or 23, for use as a medicament.

31. The use according to claim 30 wherein the medicament is vaccination or gene therapy.