for induction of expression even while corresponding DNA-based compositions did provide some level of expression.

[0009] Thus, there is a need for improved materials, formulations, production methods, and methods for delivery of CFTR mRNA for induction of CFTR expression, including in the mammalian lung, for the treatment of cystic fibrosis.

SUMMARY OF THE INVENTION

[0010] The present ~~invention~~ disclosure is based, in part, on the development of formulations of CFTR mRNA and non-naturally occurring CFTR mRNA and methods of administration thereof that can induce functional CFTR expression *in vivo*. The compositions, methods, and uses according to the disclosure ~~invention~~ can provide CFTR expression in the lung of a large mammal with a favorable safety profile suitable for effective treatment of cystic fibrosis.

[0010a] In one aspect, there is provided a use of an *in vitro* transcribed mRNA comprising a coding sequence at least 80% identical to SEQ ID NO: 3 in the manufacture of a medicament for treating cystic fibrosis in a mammal.

[0010b] In another aspect, there is provided a composition comprising an mRNA and a carrier, wherein the mRNA is an *in vitro* transcribed mRNA and has a coding sequence at least 80% identical to SEQ ID NO: 3.

[0011] Thus, in one ~~aspect~~embodiment, the present disclosure ~~invention~~ provides a method of *in vivo* production of CFTR, in particular, in the lung of a subject (e.g., a mammal) in need of delivery by delivering an mRNA encoding a CFTR protein. In some embodiments, the mRNA encoding a CFTR protein is delivered directly to the lung of the subject. As used herein, a "CFTR protein" encompasses any full length, fragment or portion of a CFTR protein which can be used to substitute for naturally-occurring CFTR protein activity and/or reduce the intensity, severity, and/or frequency of one or more symptoms associated with Cystic fibrosis. For example, a suitable CFTR protein according to the present invention may have an amino acid sequence identical to the wild-type human CFTR protein (SEQ ID NO:1). In some embodiments, a suitable CFTR protein according to the present invention may have an amino acid sequence at least about 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to the wild-type human CFTR protein (SEQ ID NO:1).

[0012] In one embodiment, the disclosure ~~invention~~ provides a method of inducing CFTR expression in epithelial cells in a lung of a mammal, the method comprising contacting the epithelial cells in the lung of the mammal with a composition, wherein: the composition is a pharmaceutical composition comprising an *in vitro* transcribed mRNA;the *in vitro* transcribed mRNA comprises a coding sequence which encodes SEQ ID NO: 1. In another embodiment, the

in vitro transcribed mRNA comprises a coding sequence which encodes an amino acid sequence at least about 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1.

[0013] In one embodiment, the ~~invention~~ disclosure provides a method of inducing CFTR expression in a mammalian target cell, the method comprising contacting the mammalian target cell with a composition, the composition comprising an *in vitro* transcribed mRNA encoding the amino acid sequence of SEQ ID NO: 1. In another embodiment, the *in vitro* transcribed mRNA comprises a coding sequence which encodes an amino acid sequence at least about 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1.

[0014] In another embodiment, the ~~invention~~ disclosure provides a non-naturally occurring mRNA molecule comprising a coding sequence, a 5'-UTR, and a 3'-UTR, wherein the coding sequence encodes the amino acid sequence of SEQ ID NO: 1 and the coding sequence is at least 80% identical to SEQ ID NO: 3. In another embodiment, the coding sequence encodes the amino acid sequence at least about 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1 and/or the coding sequence is about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 3.

[0015] In another embodiment, the ~~invention~~ disclosure provides a non-naturally occurring mRNA molecule comprising a coding sequence, a 5'-UTR, and a 3'-UTR, wherein the coding sequence encodes the amino acid sequence of SEQ ID NO: 1 and the coding sequence comprises at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the non-wild-type bases listed in Table 1 at the positions of the coding sequence listed in Table 1 relative to the wild-type coding sequence of SEQ ID NO: 2.

[0016] In another embodiment, the ~~invention~~ disclosure provides a non-naturally occurring mRNA molecule comprising a coding sequence, a 5'-UTR, and a 3'-UTR, wherein the coding sequence encodes the amino acid sequence of SEQ ID NO: 1 and the coding sequence comprises at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the non-wild-type bases listed in Table 2 at the corresponding positions of the coding sequence listed in Table 2 relative to the wild-type coding sequence of SEQ ID NO: 2.

[0017] In some embodiments, the ~~invention~~ disclosure provides a non-naturally occurring mRNA molecule comprising a coding sequence for a signal peptide. In a particular embodiment, the ~~invention~~ disclosure provides a non-naturally occurring mRNA comprising a coding sequence for a growth hormone leader sequence. In certain embodiments, the ~~invention~~ disclosure provides a non-naturally occurring mRNA comprising a coding sequence of SEQ ID NO:18 or SEQ ID NO:19. In some embodiments, the invention provides a non-naturally occurring mRNA comprising a coding sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% to SEQ ID NO:18 or SEQ ID NO:19.

[0018] In some embodiments, the ~~invention~~ disclosure provides a non-naturally occurring mRNA molecule comprising a sequence of SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ UD NO:15, SEQ ID NO:16, or SEQ ID NO:17. In some embodiments, the ~~invention~~ disclosure provides a non-naturally occurring mRNA molecule comprising a sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% to any of SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ UD NO:15, SEQ ID NO:16, or SEQ ID NO:17.

[0019] In another embodiment, the ~~invention~~ disclosure provides a polynucleotide comprising a sequence complementary to the sequence of an mRNA according to the ~~invention~~ disclosure.

[0020] In another embodiment, the ~~invention~~ disclosure provides a composition comprising the polynucleotide according to the ~~invention~~ disclosure, an RNA polymerase, and nucleoside triphosphates.

[0021] In another embodiment, the ~~invention~~ disclosure provides a pharmaceutical composition comprising an mRNA according to the ~~invention~~ disclosure.

[0022] In another embodiment, the ~~invention~~ disclosure provides a nebulization or aerosolization apparatus loaded with a pharmaceutical composition according to the ~~invention~~ disclosure.

[0023] In another embodiment, the ~~invention~~ disclosure provides a cultured cell comprising an mRNA according to the ~~invention~~ disclosure and functional CFTR expressed from the mRNA.

[0024] In another embodiment, the ~~invention~~ disclosure provides a use of a pharmaceutical composition according to the ~~invention~~ disclosure for the induction of expression of functional CFTR.

[0025] In another embodiment, the ~~invention~~ disclosure provides a method of inducing CFTR expression in epithelial cells in a lung of a mammal, the method comprising contacting the

epithelial cells with a composition, wherein the composition is a pharmaceutical composition comprising an mRNA according to the ~~invention~~ disclosure.

[0026] In another embodiment, the disclosure ~~invention~~ provides a method of inducing CFTR expression in a mammalian target cell, the method comprising contacting the mammalian target cell with a composition, the composition comprising an mRNA according to the disclosure~~invention~~.

[0027] In another embodiment, the present disclosure ~~invention~~ provides a method of treating cystic fibrosis by administering to a subject in need of treatment an mRNA encoding a CFTR protein as described herein. In one embodiment, the mRNA is administered to the lung of the subject. In one embodiment, the mRNA is administered by inhalation, nebulization, intranasal administration or aerosolization. In various embodiments, administration of the mRNA results in expression of CFTR in the lung of the subject.

[0028] In a particular embodiment, the present disclosure ~~invention~~ provides a method of treating cystic fibrosis by administering to the lung of a subject in need of treatment an mRNA comprising a coding sequence which encodes SEQ ID NO:1. In some embodiments, the present disclosure ~~invention~~ provides a method of treating cystic fibrosis by administering to the lung of a subject in need of treatment an mRNA comprising a coding sequence which encodes an amino acid sequence at least about 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to the wild-type human CFTR protein (SEQ ID NO:1). In another particular embodiment, the present disclosure ~~invention~~ provides a method of treating cystic fibrosis by administering to the lung of a subject in need of treatment an mRNA comprising a coding sequence of SEQ ID NO:3. In some embodiments, the present disclosure ~~invention~~ provides a method of treating cystic fibrosis by administering to the lung of a subject in need of treatment an mRNA comprising a coding sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:3.

[0029] In yet another ~~aspect~~embodiment, the present disclosure ~~invention~~ provides methods for making an mRNA encoding a CFTR protein as described herein. In one embodiment, the disclosure ~~invention~~ provides a method of making CFTR mRNA *in vitro*, comprising contacting an isolated polynucleotide with an RNA polymerase in the presence of nucleoside triphosphates, wherein: the isolated polynucleotide and RNA polymerase are not contained within a cell; the isolated polynucleotide is a template for the RNA polymerase; the isolated polynucleotide comprises a

promoter operably linked to a template sequence; the template sequence comprises a coding sequence complement which is complementary to a sequence encoding SEQ ID NO: 1; and: (a) the template sequence comprises fewer cryptic promoters than the complement of SEQ ID NO: 2, (b) the template sequence comprises fewer direct and/or inverted repeats than SEQ ID NO: 2, (c) the template sequence comprises complements of fewer disfavored codons than SEQ ID NO: 2, or (d) the GC content of the coding sequence complement is lower than the GC content of SEQ ID NO: 2.

[0030] In another embodiment, the disclosure ~~invention~~ provides a method of making CFTR mRNA *in vitro*, comprising contacting an isolated polynucleotide according to the disclosure ~~invention~~ with an RNA polymerase in the presence of nucleoside triphosphates, wherein: the isolated polynucleotide and RNA polymerase are not contained within a cell; the isolated polynucleotide is a template for the RNA polymerase; and the isolated polynucleotide comprises a promoter operably linked to a template sequence, and the RNA polymerase synthesizes mRNA comprising a coding sequence encoding SEQ ID NO: 1.

[0031] In some embodiments of such uses and methods of treatment, the *in vitro* transcribed mRNA is a naturally occurring or wild-type mRNA encoding human CFTR (SEQ ID NO: 2) modified to include non-naturally occurring UTRs. In other embodiments, the *in vitro* transcribed mRNA is a non-naturally occurring mRNA as described above.

[0032] Additional objects and advantages of the disclosure ~~invention~~ will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and advantages of the disclosure ~~invention~~ will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

[0033] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the disclosure~~invention~~, as claimed.

[0034] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the disclosure~~invention~~.

CLAIMS

We Claim:

1. A method of inducing CFTR expression in epithelial cells in a lung of a mammal, the method comprising contacting the epithelial cells in the lung of the mammal with a composition, wherein:
the composition is a pharmaceutical composition comprising an *in vitro* transcribed mRNA;
the *in vitro* transcribed mRNA comprises a coding sequence which encodes SEQ ID NO: 1.

2. A method of inducing CFTR expression in a mammalian target cell,
the method comprising contacting the mammalian target cell with a composition,
the composition comprising an *in vitro* transcribed mRNA encoding the amino acid sequence of SEQ ID NO: 1.

3. The method of claim 1 or claim 2, wherein:
(a) the *in vitro* transcribed mRNA sequence comprises fewer complements of cryptic promoters than SEQ ID NO: 2,
(b) the *in vitro* transcribed mRNA sequence comprises fewer direct and/or inverted repeats than SEQ ID NO: 2,
(c) the coding sequence comprises fewer disfavored codons than SEQ ID NO: 2, and/or
(d) the GC content of the coding sequence is lower than the GC content of SEQ ID NO: 2.

4. A non-naturally occurring mRNA molecule comprising a coding sequence, a 5'-UTR, and a 3'-UTR, wherein the coding sequence encodes the amino acid sequence of SEQ ID NO: 1 and the coding sequence is at least 80% identical to SEQ ID NO: 3.

5. A non-naturally occurring mRNA molecule comprising a coding sequence, a 5'-UTR, and a 3'-UTR, wherein the coding sequence encodes the amino acid sequence of SEQ ID NO: 1 and the coding sequence comprises at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% of the non-wild-type bases listed in Table 1 at the positions of the coding sequence listed in Table 1 relative to the wild-type coding sequence of SEQ ID NO: 2.

6. A non-naturally occurring mRNA molecule comprising a coding sequence, a 5'-UTR, and a 3'-UTR, wherein the coding sequence encodes the amino acid sequence of SEQ ID NO: 1 and the coding sequence comprises at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% of the non-wild-type bases listed in Table 2 at the corresponding positions of the coding sequence listed in Table 2 relative to the wild-type coding sequence of SEQ ID NO: 2.

7. The mRNA molecule of any one of claims 4 to 6, wherein the coding sequence is at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identical to SEQ ID NO: 3.

8. The mRNA molecule of claim 4, wherein the coding sequence is identical to SEQ ID NO: 3.

9. The mRNA molecule of any one of claims 4 to 8, wherein the 5'-UTR comprises SEQ ID NO: 4 and/or the 3'-UTR comprises SEQ ID NO: 5.

10. The mRNA molecule of any one of claims 4 to 9, further comprising a poly-A tail of at least 70, 100, 120, 150, 200, or 250 residues in length.

11. The mRNA molecule of any one of claims 4 to 10, further comprising a 5' cap.

12. The mRNA molecule of any one of claims 4 to 11, wherein at least one constituent nucleotide is a locked nucleic acid residue.

13. The mRNA molecule of any one of claims 4 to 12, wherein the mRNA comprises at least one nonstandard nucleobase.

14. The mRNA molecule of claim 13, wherein the nonstandard nucleobase is chosen from one or more of 5-methyl-cytidine, pseudouridine, and 2-thio-uridine.

15. The mRNA molecule of any one of claims 4 to 14, for use in inducing functional CFTR expression in a mammal or a mammalian cell.

16. A polynucleotide comprising a sequence complementary to the sequence of the mRNA of any one of claims 4 to 15.

17. The polynucleotide of claim 16, wherein the polynucleotide is a linear or circular polynucleotide comprising deoxyribonucleotide residues.

18. A composition comprising the polynucleotide of claim 16 or claim 17, an RNA polymerase, and nucleoside triphosphates.

19. A pharmaceutical composition comprising the mRNA of any one of claims 4 to 15.

20. The pharmaceutical composition of claim 19, further comprising an organic cation chosen from polyethyleneimine (PEI), protamine, PEGylated protamine, PLL, PEGylated PLL, or a cationic lipid, wherein the organic cation is non-covalently complexed with the mRNA.

21. The pharmaceutical composition of claim 20, wherein the organic cation is a cationic lipid and the composition further comprises a neutral lipid, a pegylated lipid, and/or cholesterol.

22. The pharmaceutical composition of claim 21, wherein the cationic lipid is chosen from DODAP (1,2-dioleyl-3-dimethylammonium propane) , DLinDMA, DLin-KC2-DMA, C12-200, HGT4003, HGT5000, HGT5001, MC3, ICE, a cationic lipid comprising a dialkylamino moiety, a cationic lipid comprising an imidazole moiety, and a cationic lipid comprising a guanidinium moiety.

23. The pharmaceutical composition of any one of claims 21 or 22, wherein the neutral lipid is present in the composition and is chosen from DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), DPPC (1,2-dipalmitoyl-sn-glycero-3-phosphocholine), DOPE (1,2-dioleyl-sn-glycero-3-phosphoethanolamine), DPPE (1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine), DMPE (1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine), and DOPG (,2-dioleoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol)).

24. The pharmaceutical composition of any one of claims 21 to 23, wherein the pegylated lipid is present in the composition and comprises one or more alkyl

chain(s) of C_6-C_{20} length covalently attached to a poly(ethylene) glycol chain of up to 5 kDa in length.

25. The pharmaceutical composition of claim 20, wherein the organic cation is branched PEI with a molecular weight ranging from 10 kDa to 40 kDa.

26. A nebulization or aerosolization apparatus loaded with the pharmaceutical composition of any one of claims 19 to 25.

27. A cultured cell comprising the mRNA of any one of claims 4 to 15 and functional CFTR expressed from the mRNA.

28. The cultured cell of claim 27, which does not comprise genomic DNA encoding wild-type human CFTR or cDNA encoding wild-type human CFTR.

29. Use of the pharmaceutical composition of any one of claims 19 to 25 for the induction of expression of functional CFTR.

30. A method of inducing CFTR expression in epithelial cells in a lung of a mammal, the method comprising contacting the epithelial cells with a composition, wherein the composition is a pharmaceutical composition comprising the mRNA of any one of claims 4 to 15.

31. A method of inducing CFTR expression in a mammalian target cell, the method comprising contacting the mammalian target cell with a composition, the composition comprising the mRNA of any one of claims 4 to 15.

32. The method of any one of claims 1 to 3 or 29 to 31, wherein the composition further comprises an organic cation chosen from polyethyleneimine (PEI) or a cationic lipid, wherein the organic cation is non-covalently complexed with the *in vitro* transcribed mRNA.

33. The method of any one of claims 1 to 3 or 29 to 32, wherein the composition does not comprise a mucolytic agent.

34. The method of any one of claims 1 to 3 or 29 to 33, wherein the organic cation is a cationic lipid and the composition further comprises a neutral lipid, a pegylated lipid, and/or cholesterol.

35. The method of any one of claims 1 to 3 or 29 to 34, wherein the cationic lipid is chosen from chosen from DOTAP (1,2-dioleyl-3-trimethylammonium propane), DODAP (1,2-dioleyl-3-dimethylammonium propane) , DOTMA (1,2-di-O-octadecenyl-3-trimethylammonium propane), DLinDMA, DLin-KC2-DMA, C12-200, HGT4003, HGT5000, HGT5001, MC3, ICE, a cationic lipid comprising a dialkylamino moiety, a cationic lipid comprising an imidazole moiety, and a cationic lipid comprising a guanidinium moiety.

36. The method of any one of claims 1 to 3 or 29 to 35, wherein the neutral lipid is present in the composition and is chosen from DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), DPPC (1,2-dipalmitoyl-sn-glycero-3-phosphocholine), DOPE (1,2-dioleyl-sn-glycero-3-phosphoethanolamine), DPPE (1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine), DMPE (1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine), and DOPG (,2-dioleoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol)).

37. The method of any one of claims 1 to 3 or 29 to 36, wherein the pegylated lipid is present in the composition and comprises one or more alkyl chain(s) of C_6-C_{20} length covalently attached to a poly(ethylene) glycol chain of up to 5 kDa in length.

38. The method of any one of claims 1 to 3 or 29 to 37, wherein the organic cation is branched PEI with a molecular weight ranging from 10 kDa to 40 kDa.

39. The method of any one of claims 1 to 3 or 29 to 38, wherein the composition is administered via nebulization or aerosolization.

40. A method of making CFTR mRNA *in vitro*, comprising contacting an isolated polynucleotide with an RNA polymerase in the presence of nucleoside triphosphates, wherein:

the isolated polynucleotide and RNA polymerase are not contained within a cell;

the isolated polynucleotide is a template for the RNA polymerase;

the isolated polynucleotide comprises a promoter operably linked to a template sequence;

the template sequence comprises a coding sequence complement which is complementary to a sequence encoding SEQ ID NO: 1; and:

(a) the template sequence comprises fewer cryptic promoters than the complement of SEQ ID NO: 2, (b) the template sequence comprises fewer direct and/or inverted repeats than SEQ ID NO: 2, (c) the template sequence comprises complements of fewer disfavored codons than SEQ ID NO: 2, or (d) the GC content of the coding sequence complement is lower than the GC content of SEQ ID NO: 2.

41. A method of making CFTR mRNA *in vitro*, comprising contacting the isolated polynucleotide of any one of claims 16 or 17 with an RNA polymerase in the presence of nucleoside triphosphates, wherein:
the isolated polynucleotide and RNA polymerase are not contained within a cell;
the isolated polynucleotide is a template for the RNA polymerase; and
the isolated polynucleotide comprises a promoter operably linked to a template sequence,
and the RNA polymerase synthesizes mRNA comprising a coding sequence encoding SEQ ID NO: 1.

42. The method of any one of claims 40 to 41, wherein the RNA polymerase is T7 RNA polymerase.

43. The method of any one of claims 40 to 42, wherein the nucleoside triphosphates comprise one or more of pseudouridine triphosphate, 5-methyl-cytidine triphosphate, and 2-thio-uridine triphosphate.

44. The method of any one of claims 40 to 43, further comprising isolating the mRNA comprising a coding sequence encoding SEQ ID NO: 1.

45. The method of claim 44, further comprising adding a 5' cap to the isolated mRNA.

46. The method of claim 45, further comprising formulating a pharmaceutical composition by contacting the capped isolated mRNA with one or more pharmaceutically acceptable carriers comprising one or more organic cations.

47. The method of claim 46, wherein the one or more organic cations comprise polyethyleneimine (PEI), protamine, PEGylated protamine, PLL, PEGylated PLL, or a cationic lipid.

CLAIMS

1. Use of an *in vitro* transcribed mRNA comprising a coding sequence at least 80% identical to SEQ ID NO: 3 in the manufacture of a medicament for treating cystic fibrosis in a mammal.

2. The use according to claim 1, wherein the coding sequence is at least 90% identical to SEQ ID NO: 3.

3. The use according to claim 1, wherein the coding sequence is 100% identical to SEQ ID NO: 3.

4. The use according to any one of the preceding claims, wherein the mRNA comprises a 5' untranslated region (UTR), a 3' UTR, a signal peptide coding sequence, a cap structure and/or a tail structure.

5. The use according to claim 4, wherein the 5'-UTR comprises SEQ ID NO: 4 and/or the 3'-UTR comprises SEQ ID NO: 5.

6. The use according to claim 4 or 5, wherein the tail structure is a poly-A tail of at least 70, 100, 120, 150, 200, or 250 residues in length.

7. The use according to any one of claims 4-6, wherein the cap structure is a cap1 structure.

8. The use according to any one of the preceding claims, wherein the mRNA comprises one or more nonstandard nucleotide(s), optionally wherein the one or more nonstandard nucleotide(s) is/are chosen from 5-methyl-cytidine, pseudouridine, and 2-thio-uridine.

9. The use according to any one of the preceding claims, wherein the medicament is to be administered to the lung of the mammal by inhalation, intranasal administration, aerosolization, or nebulization.

10. The use according to any one of the preceding claims, wherein the mRNA comprises a coding sequence which encodes a human cystic fibrosis transmembrane conductance regulator (CFTR) protein of SEQ ID NO:1, optionally wherein the human CFTR protein is expressed in the epithelial cells of the lung.

11. The use according to any one of the preceding claims, wherein the medicament is to be administered with a carrier.

12. The use according to claim 11, wherein the carrier comprises an organic cation, such as a cationic lipid or a cationic organic polymer.

13. The use according to claim 12, wherein the cationic organic polymer is selected from the group consisting of polyethyleneimine (PEI), protamine, PEGylated protamine, poly-L-lysine (PLL), and PEGylated PLL.

14. The use according to claim 13, wherein the PEI is branched PEI with a molecular weight ranging from 10 kDa to 40 kDa.

15. The use according to any one of claims 11-14, wherein the carrier is a liposome.

16. A composition comprising an mRNA and a carrier, wherein the mRNA is an *in vitro* transcribed mRNA and has a coding sequence at least 80% identical to SEQ ID NO: 3.

17. The composition of claim 16, wherein the carrier comprises an organic cation, such as a cationic lipid or a cationic organic polymer.

18. The composition according to claim 17, wherein the cationic organic polymer is selected from the group consisting of polyethyleneimine (PEI), protamine, PEGylated protamine, poly-L-lysine (PLL), and PEGylated PLL.

19. The composition according to claim 18, wherein the PEI is branched PEI with a molecular weight ranging from 10 kDa to 40 kDa.

20. The composition of claim 16, wherein the carrier is a liposome.