Claims

1. A method of delivering a heterologous nucleic acid to a lung cell in a subject comprising administering to the subject a composition comprising a recombinant adeno-associated virus (rAAV) vector, said rAAV vector comprising (i) a capsid comprising a capsid protein comprising the amino acid sequence as set forth as SEQ ID NO:12 or an amino acid sequence at least 90% identical to SEQ ID NO: 12 and comprising a Thr at amino acid 469 and an Ala at amino acid 598 based on the amino acid numbering set forth in SEQ ID NO: 12 and (ii) a heterologous nucleic acid comprising a nucleotide sequence encoding a gene product, whereby the step of administering comprises pulmonary, endobronchial, intranasal, intratracheal, and/or intrabronchial administration.

2 The method according to claim 1, wherein the lung cell is selected from an airway epithelial cell, a smooth muscle cell, and an endothelial cell.

3. The method according to claim 2, wherein the airway epithelial cell is a basal cell, a goblet cell or a cilia cell.

4. The method according to claim 3, wherein the airway epithelial cell is a lung alveolar epithelial type 1 (AECI), a lung alveolar type 2 (AECII) cell, a bronchial epithelial cell or a tracheal epithelial cell.

5. The method according to any one of claims 1-4, wherein the composition is formulated as an aerosol.

6. The method according to claim 5, wherein the method comprises administering the composition by a nebulizer.

7. The method according to any one of claims 1-6, wherein the composition comprises 10^{11} to 10^{14} vector genomes (vg) of the rAAV per ml.

8. The method according to any one of claims 1-7, wherein the nucleotide sequence encoding the gene product is operably linked to a promoter.

9. The method according to claim 8, wherein the promoter is a constitutive promoter.

10. The method according to claim 8, wherein the promoter is a tissue-specific promoter.

11. The method according to any one of claims 1-10, wherein the heterologous nucleic acid comprises a nucleotide sequence encoding a gene product selected from: cystic fibrosis transmembrane conductance regulator (CFTR protein) or a biologically active fragment thereof, SFTPA1 (surfactant A1), Caveolin-1, alpha-1-antitrypsin, alpha-1-antichymotrypsin, alpha-1-macroglobulin, matrix metalloproteinase 1 (MMP1), matrix metalloproteinase 12 (MMP12), microsomal epoxide hydrolyase, CYP1A1, Glutathione S-transferase, heme oxygenase-1, TGF-beta-1, TNF-alpha, IL-1 complex, IL-8, IL-13, human leukocyte antigen, vitamin D binding protein, beta-2-adrenergic receptor.

12. The method according to claim 11, wherein the gene product is a human cystic fibrosis transmembrane conductance regulator (CFTR) protein or a biologically active truncated CFTR protein lacking amino acids 708-759 of the human CFTR protein sequence.

13. The method according to claim 12, wherein the gene product is a biologically truncated CFTR protein lacking amino acids 708-759 of the human CFTR protein sequence.

14. The method according to claim 13, wherein the heterologous nucleic acid comprises the nucleotide sequence set forth in SEQ ID NO:43 or a sequence at least 80% identical thereto.

15. A pharmaceutical composition comprising an rAAV vector, said rAAV vector comprising (i) a capsid comprising a capsid protein of SEQ ID NO:12 or an amino acid sequence at least 90% identical to SEQ ID NO:12 and comprising a Thr at amino acid 469 and an Ala at amino acid 598 based on the amino acid numbering set forth in SEQ ID NO: 12 and (ii) a heterologous nucleic acid comprising a nucleotide sequence encoding a CFTR or a biologically active truncated CFTR protein lacking amino acids 708-759 of the human CFTR protein sequence, said nucleotide sequence operably linked to an expression control sequence.

16. The pharmaceutical composition according to claim 15, wherein the nucleotide sequence encoding the CFTR protein is at least 80% identical to the nucleotide sequence set forth as SEQ ID NO:43.

17. The pharmaceutical composition according to claim 16, wherein the nucleotide sequence encoding the CFTR comprises the nucleotide sequence set forth as SEQ ID NO:43.

18. The pharmaceutical composition according to any one of claims 15-17, wherein the expression control sequence comprises a ubiquitous promoter, preferably wherein the ubiquitous promoter is a CMV173.

19. The pharmaceutical composition according to any one of claims 15-18, wherein the composition is formulated for inhalation or is suitable for inhalation.

20. The pharmaceutical composition according to any one of claims 15 to 19, comprising about 20 mM to about 50 mM citrate, about 85 mM to about 125 mM NaCl and about 0.005% Pluronic F68 and having a pH of about 6.0.

21. The pharmaceutical composition according to claim 20, comprising about 20 mM citrate, about 125 mM NaCl and about 0.005% Pluronic F68 and having a pH of about 6.0.

22. The pharmaceutical composition according to any one of claims 15-21 for use in therapy.

23. The use of a pharmaceutical composition according to any one of claims 15-21, in the manufacture of a medicament for the treatment of cystic fibrosis, wherein the pharmaceutical composition is for pulmonary, endobronchial, intranasal, intratracheal, and/or intrabronchial administration.

24. Use of a composition comprising a recombinant adeno-associated virus (rAAV) vector in the manufacture of a medicament for the treatment of lung disorder, wherein a heterologous nucleic acid is to be delivered to a lung cell in a subject, wherein said rAAV vector comprises (i) a capsid comprising a capsid protein comprising the amino acid sequence set forth as SEQ ID NO:12 or an amino acid sequence at least 90% identical to SEQ ID NO:12 and comprising a Thr at amino acid 469 and an Ala at amino acid 598 based on the amino acid numbering set forth in SEQ ID NO: 12 and (ii) a heterologous nucleic acid comprising a nucleotide sequence encoding a gene product, wherein the composition is to be administered by pulmonary, endobronchial, intranasal, intratracheal, and/or intrabronchial administration.

25. The use according claim 24, wherein the composition is to be used in the treatment of cystic fibrosis, pulmonary disease, or a lung disease associated therewith.

26. The use according to claim 25, wherein the composition is to be used in the treatment of cystic fibrosis.

27. The method according to claim 1, wherein the capsid protein comprises an amino acid sequence at least 96% identical to SEQ ID NO: 12.

28. The method according to claim 1, wherein the capsid protein comprises an amino acid sequence at least 97% identical to SEQ ID NO: 12.

29. The pharmaceutical composition according to claim 15, wherein the capsid protein comprises an amino acid sequence at least 98% identical to SEQ ID NO: 12.

30. The pharmaceutical composition according to claim 15, wherein the capsid protein comprises an amino acid sequence at least 99% identical to SEQ ID NO: 12.