Claims

1. Use of a recombinant adeno-associated virus (rAAV) vector in the manufacture of a composition for the treatment of a lung disorder in a subject, wherein the composition is for delivering a heterologous nucleic acid to a lung cell in the subject, 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 98% 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 therapeutic protein or an RNA interfering (RNAi) agent, wherein the composition is formulated for pulmonary, endobronchial, intranasal, intratracheal, and/or intrabronchial administration.

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

4. The use according to claim 2, 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 use according to any one of claims 1-4, wherein the composition is formulated as an aerosol.

6. The use according to claim 5, wherein the composition is for administration by a nebulizer.

7. The use 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 use according to any one of claims 1-7, wherein the nucleotide sequence encoding the therapeutic protein or RNAi agent is operably linked to a promoter.

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

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

11. The use according to any one of claims 1-10, wherein the therapeutic protein is 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 use according to claim 11, wherein the therapeutic protein 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 use according to claim 12, wherein the therapeutic protein is a biologically active truncated CFTR protein lacking amino acids 708-759 of the human CFTR protein sequence.

14. The use 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 98% 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 said nucleotide sequence 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 said nucleotide sequence 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 20 mM to 50 mM citrate, 85 mM to 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 recombinant adeno-associated virus (rAAV) vector in the manufacture of a composition for the treatment of cystic fibrosis or alpha-1-antitrypsin deficiency, 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 98% 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 therapeutic protein or an RNA interfering (RNAi) agent, wherein the composition is to be administered by pulmonary, endobronchial, intranasal, intratracheal, and/or intrabronchial administration.

25. The use according to claim 24, wherein the composition is to be used in the treatment of cystic fibrosis.

26. The use according to any one of claims 1 to 14 and 24 to 25, wherein the capsid protein comprises an amino acid sequence at least 99% identical to SEQ ID NO: 12.

27. The use according to any one of claims 1 to 14 and 24 to 25, wherein the capsid protein comprises the amino acid sequence set forth as SEQ ID NO: 12.

28. The pharmaceutical composition according to any one of claims 15 to 21, wherein the capsid protein comprises an amino acid sequence at least 99% identical to SEQ ID NO: 12.

29. The pharmaceutical composition according to any one of claims 15 to 21, wherein the capsid protein comprises the amino acid sequence set forth as SEQ ID NO: 12.