CLAIMS

1. A recombinant adeno-associated virus (rAAV) comprising (i) an AV.TL65 capsid protein ~~or a variant thereof~~, the AV.TL65 capsid protein having at least 80% amino acid sequence identity to SEQ ID NO:13; and (ii) a polynucleotide comprising an F5 enhancer, the F5 enhancer having at least 80% nucleic acid sequence identity to SEQ ID NO:14, ~~or a variant thereof,~~ and a tg83 promoter, the tg83 promoter having at least 80% nucleic acid sequence identity to SEQ ID NO:2, ~~or a variant thereof~~, operably linked to a CFTRΔR minigene ~~or a variant thereof~~.

2. The rAAV of claim 1, wherein the AV.TL65 capsid protein has at least 95% amino acid sequence identity to SEQ ID NO:13.

3. The rAAV of claim 2, wherein the AV.TL65 capsid protein has at least 99% amino acid sequence identity to SEQ ID NO:13.

4~~2~~. The rAAV of claim 3~~1~~, wherein the AV.TL65 capsid protein comprises the amino acid sequence of SEQ ID NO:13 ~~or the variant comprises at least 80% amino acid sequence identity to SEQ ID NO:13~~.

5~~3~~. The rAAV of any one of claims 1 to 4 ~~or 2~~, wherein the F5 enhancer comprises the polynucleotide sequence of SEQ ID NO:1 ~~or the variant thereof comprises at least 80% nucleic acid sequence identity to SEQ ID NO:1~~.

6. The rAAV of any one of claims 1 to 4, wherein the F5 enhancer has at least 95% nucleic acid sequence identity to SEQ ID NO:14.

7. The rAAV of claim 6, wherein the F5 enhancer has at least 99% nucleic acid sequence identity to SEQ ID NO:14.

8~~4~~. The rAAV of claim 7~~1 or 2~~, wherein the F5 enhancer comprises the polynucleotide sequence of SEQ ID NO:14 ~~or the variant thereof comprises at least 80% nucleic acid sequence identity to SEQ ID NO:14~~.

9. The rAAV of any one of claims 1 to 8, wherein the tg83 promoter has at least 95% nucleic acid sequence identity to SEQ ID NO:2.

10. The rAAV of claim 9, wherein the tg83 promoter has at least 99% nucleic acid sequence identity to SEQ ID NO:2.

11~~5~~. The rAAV of ~~any one of~~ claim~~s~~ 10 ~~to 4~~, wherein the tg83 promoter comprises the polynucleotide sequence of SEQ ID NO:2 ~~or the variant thereof comprises at least 80% nucleic acid sequence identity to SEQ ID NO:2~~.

12~~6~~. The rAAV of any one of claims 1 to 11~~5~~, wherein the CFTRΔR minigene is a human CFTRΔR minigene.

13~~7~~. The rAAV of claim 12~~6~~, wherein the human CFTRΔR minigene is encoded by a polynucleotide ~~comprising the sequence of SEQ ID NO:4 or~~ having~~the variant thereof comprising~~ at least 80% nucleic acid sequence identity to SEQ ID NO:4.

14. The rAAV of claim 13, wherein the human CFTRΔR minigene is encoded by a polynucleotide having at least 95% nucleic acid sequence identity to SEQ ID NO:4.

15. The rAAV of claim 14, wherein the human CFTRΔR minigene is encoded by a polynucleotide having at least 99% nucleic acid sequence identity to SEQ ID NO:4.

16. The rAAV of claim 15, wherein the human CFTRΔR minigene is encoded by a polynucleotide comprising the nucleic acid sequence of SEQ ID NO:4.

17~~8~~. The rAAV of any one of claims 1 to 16~~7~~, wherein the polynucleotide comprises, in a 5'-to-3' direction, the F5 enhancer, the tg83 promoter, and the CFTRΔR minigene.

18. The rAAV of any one of claims 1 to 17, wherein the polynucleotide comprises, in a 5'-to-3' direction, the AV.TL65 capsid protein comprising the amino acid sequence of SEQ ID NO:13, the F5 enhancer comprising the polynucleotide sequence of SEQ ID NO:14, the tg83 promoter comprising the polynucleotide sequence of SEQ ID NO:2, and the human CFTRΔR minigene encoded by a polynucleotide comprising the nucleic acid sequence of SEQ ID NO:4.

19. An rAAV comprising, in a 5'-to-3' direction, (i) an AV.TL65 capsid protein comprising the amino acid sequence of SEQ ID NO:13; and (ii) an isolated polynucleotide comprising the sequence of SEQ ID NO:7.

209. A pharmaceutical composition comprising the rAAV of any one of claims 1 to 198 and a pharmaceutically acceptable carrier.

2110. Use of the rAAV of any one of claims 1 to -198 or the pharmaceutical composition of claim 209 in the manufacture of a medicament for treating cystic fibrosis.

2211. The use of claim 2110, wherein the medicament is formulated for administration in combination with one or more additional therapeutic agents.

2312. The use of claim 2211, wherein the one or more additional therapeutic agents includes an antibiotic, a mucus thinner, a CFTR modulator, a mucolytic, normal saline, hypertonic saline, an immunosuppressive agent, or a combination thereof.

2413. The use of any one of claims 2110 to 2312, wherein the medicament is formulated for administration by inhalation, by nebulization, or by aerosolization, or by intranasal, intratracheal, intrabronchial, oral, intravenous, subcutaneous, or intramuscular administration.

2514. The use of claim 2413, wherein the medicament is formulated for administration by inhalation, by nebulization, or by aerosolization, or by intranasal, intratracheal, and/or intrabronchial administration.

2615. The rAAV of any one of claims 1-198 or the pharmaceutical composition of claim 209 for use in treating cystic fibrosis.

2716. The rAAV for use or the pharmaceutical composition for use of claim 2615, wherein the rAAV or the pharmaceutical composition is formulated for administration in combination with one or more additional therapeutic agents.

2817. The rAAV for use or the pharmaceutical composition for use of claim 2716, wherein the one or more additional therapeutic agents includes an antibiotic, a mucus thinner, a CFTR modulator, a mucolytic, normal saline, hypertonic saline, an immunosuppressive agent, or a combination thereof.

2918. The rAAV for use or the pharmaceutical composition for use of any one of claims 2615 to 2817, wherein the rAAV or the pharmaceutical composition is formulated for administration by inhalation, by nebulization, or by aerosolization, or by intranasal, intratracheal, intrabronchial, oral, intravenous, subcutaneous, or intramuscular administration.

3019. The rAAV for use or the pharmaceutical composition for use of claim 2918, wherein the rAAV or the pharmaceutical composition is formulated for administration by inhalation, by nebulization, or by aerosolization, or by intranasal, intratracheal, and/or intrabronchial administration.

20. An isolated polynucleotide comprising the sequence of SEQ ID NO:7 or a variant thereof with at least 80% nucleic acid sequence identity to SEQ ID NO:7.

3121. The rAAVpolynucleotide of claim 1920, further comprising, in the 3' direction, a 3' untranslated region (3'-UTR) comprising the sequence of SEQ ID NO:5 or a variant thereof with at least 80% nucleic acid sequence identity to SEQ ID NO:5.

3222. The rAAVpolynucleotide of claim 1920 or 3121 further comprising, in the 3' direction, a synthetic polyadenylation site comprising the sequence of SEQ ID NO:6 or a variant thereof with at least 80% nucleic acid sequence identity to SEQ ID NO:6.

3323. The rAAVpolynucleotide of any one of claims 19, 31, and 3220 to 22, further comprising a 5' adeno-associated virus (AAV) inverted terminal repeat at the 5' terminus of the polynucleotide and a 3' AAV ITR at the 3' terminus of the polynucleotide.

3424. The rAAVpolynucleotide of claim 3323, wherein the polynucleotide comprises the sequence of SEQ ID NO:17 or a variant thereof with at least 80% nucleic acid sequence identity to SEQ ID NO:17.

25. A recombinant adeno-associated virus (rAAV) comprising the polynucleotide of any one of claims 20 to 24.

26. The rAAV of claim 25, wherein the rAAV has a tropism for airway epithelial cells.

27. The rAAV of claim 26, wherein the rAAV has a tropism for lung epithelial cells.

28. The rAAV of any one of claims 25 to 27, wherein the rAAV comprises an AV.TL65 capsid protein, an AAV1 capsid protein, an AAV2 capsid protein, an AAV5 capsid protein, an AAV6 capsid protein, or an AAV9 capsid protein.

29. The rAAV of claim 28, wherein the rAAV comprises an AV.TL65 capsid protein.