CLAIMS

1. A recombinant adeno-associated virus (rAAV) comprising (i) an AV.TL65 capsid protein or a variant thereof; and (ii) a polynucleotide comprising an F5 enhancer, or a variant thereof, and a tg83 promoter, 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 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.

3. The rAAV of claim 1 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.

4. The rAAV of claim 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.

5. The rAAV of any one of claims 1 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.

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

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

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

9. A pharmaceutical composition comprising the rAAV of any one of claims 1 to 8 and a pharmaceutically acceptable carrier.

10. Use of the rAAV of any one of claims 1-8 or the pharmaceutical composition of claim 9 in the manufacture of a medicament for treating cystic fibrosis.

11. The use of claim 10, wherein the medicament is formulated for administration in combination with one or more additional therapeutic agents.

12. The use of claim 11, 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.

13. The use of any one of claims 10 to 12, 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.

14. The use of claim 13, wherein the medicament is formulated for administration by inhalation, by nebulization, or by aerosolization, or by intranasal, intratracheal, and/or intrabronchial administration.

15. The rAAV of any one of claims 1-8 or the pharmaceutical composition of claim 9 for use in treating cystic fibrosis.

16. The rAAV for use or the pharmaceutical composition for use of claim 15, wherein the rAAV or the pharmaceutical composition is formulated for administration in combination with one or more additional therapeutic agents.

17. The rAAV for use or the pharmaceutical composition for use of claim 16, 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.

18. The rAAV for use or the pharmaceutical composition for use of any one of claims 15 to 17, 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.

19. The rAAV for use or the pharmaceutical composition for use of claim 18, 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.

21. The polynucleotide of claim 20, 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.

22. The polynucleotide of claim 20 or 21 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.

23. The polynucleotide of any one of claims 20 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.

24. The polynucleotide of claim 23, 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.