CLAIMS

1. A retroviral vector comprising a modified retroviral RNA sequence which is:

(i) codon-substitution; and

(ii) comprises a reduced number of retroviral open reading frames (ORFs)

compared with the non-modified retroviral RNA sequence from which the modified retroviral RNA sequence is derived;

and wherein:

(a) the retroviral RNA sequence comprises a promoter and a transgene; and

(b) the retroviral vector is pseudotyped with hemagglutinin-neuraminidase (HN) and fusion (F) proteins from a respiratory paramyxovirus.

2. The retroviral vector of claim 1, wherein compared with the non-modified retroviral RNA sequence from which the modified retroviral RNA sequence is derived, the modified retroviral RNA sequence is lacking:

(a) one or more retroviral ORFs 5' of the promoter:

(b) one or more retroviral ORF encoding a peptide of ≥ 100 amino acids in length;

(c) one or more retroviral ORF comprised in a partial *RRE* sequence; and/or

(d) one or more retroviral ORF encoded comprised in a partial *Gag* sequence.

3. The retroviral vector of claim 1 or 2, wherein:

a. the respiratory paramyxovirus is a Sendai virus;

b. the promoter is selected from the group consisting of a hybrid human CMV enhancer/EF1a (hCEF) promoter, a cytomegalovirus (CMV) promoter, and elongation factor 1a (EF1a) promoter; optionally wherein the vector comprises a hybrid human CMV enhancer/EF1a (hCEF) promoter; and/or

c. the retroviral vector is an SIV vector.

4. The retroviral vector of any one of the preceding claims, wherein the transgene is selected from:

a) *CFTR*, *ABCA3*, *DNAH5*, *DNAH11*, *DNAI1*, and *DNAI2*; or

b) a secreted therapeutic protein, optionally Alpha-1 Antitrypsin (A1AT), Factor VIII, Surfactant Protein B (SFTPB), Factor VII, Factor IX, Factor X, Factor XI, von Willebrand Factor, Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) and a monoclonal antibody against an infectious agent.

5. The retroviral vector of any one of the preceding claims, wherein the transgene encodes:

a) CFTR;

b) A1AT; or

c) FVIII.

6. The retroviral vector of any one of the preceding claims, wherein:

a) the promoter is a hCEF promoter and the transgene encodes CFTR;

b) the promoter is a hCEF promoter and the transgene encodes A1AT; or

c) the promoter is a hCEF or CMV promoter and the transgene encodes FVIII.

7. The retroviral vector of any one of the preceding claims, which is a lentiviral vector; optionally wherein the lentiviral vector is selected from the group consisting of a Simian immunodeficiency virus (SIV) vector, a Human immunodeficiency virus (HIV) vector, a Feline immunodeficiency virus (FIV) vector, an Equine infectious anaemia virus (EIAV) vector, and a Visna/maedi virus vector.

8. The retroviral vector of any one of the preceding claims, wherein the modified retroviral RNA sequence (i) is less than 9,000 bases in length and; (ii) comprises or consists of a nucleic acid sequence having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or up to 100% identity to SEQ ID NO: 1.

9. The retroviral vector of claim 8, wherein the modified retroviral RNA sequence comprises or consists of a nucleic acid sequence of SEQ ID NO: 1, preferably wherein the modified retroviral RNA sequence consists of a nucleic acid sequence of SEQ ID NO: 1.

10. The retroviral vector of any one of the preceding claims, wherein the vector further comprises one or more of:

(a) a p17 protein comprising or consisting of an amino acid sequence having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or up to 100% sequence identity to SEQ ID NO: 2;

(b) a p24 protein comprising or consisting of an amino acid sequence having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or up to 100% sequence identity to SEQ ID NO: 3;

(c) p8 protein comprising or consisting of an amino acid sequence having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or up to 100% sequence identity to SEQ ID NO: 4;

(d) a protease comprising or consisting of an amino acid sequence having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or up to 100% sequence identity to SEQ ID NO: 5;

(e) a p51 protein comprising or consisting of an amino acid sequence having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or up to 100% sequence identity to SEQ ID NO: 6;

(f) a p15 protein comprising or consisting of an amino acid sequence having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or up to 100% sequence identity to SEQ ID NO: 7; and

(g) a p31 protein comprising or consisting of an amino acid sequence having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or up to 100% sequence identity to SEQ ID NO: 8;

wherein optionally the vector comprises each of (a) to (g).

11. The retroviral vector of any one of the preceding claims, wherein the vector further comprises one or more of:

(a) a Gag protein comprising or consisting of an amino acid sequence having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or up to 100% sequence identity to SEQ ID NO: 9; and/or

(b) a Pol protein comprising or consisting of an amino acid sequence having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or up to 100% sequence identity to SEQ ID NO: 10.

12. The retroviral vector of any one of the preceding claims, wherein the F protein is an Fct4 protein, which optionally:

(a) comprises or consists of an amino acid sequence having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or up to 100% sequence identity to SEQ ID NO: 12 or 13; and/or

(b) is cleaved into two subunits, wherein optionally a first subunit comprises or consists of an amino acid sequence having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or up to 100% sequence identity to SEQ ID NO: 14 and a second subunit comprises or consists of an amino acid sequence having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or up to 100% sequence identity to SEQ ID NO: 15.

13. A SIV vector pseudotyped with Sendai virus hemagglutinin-neuraminidase (HN) and fusion (F) proteins, wherein:

(a) said vector comprises a modified retroviral RNA sequence which comprises or consists of a nucleic acid sequence of SEQ ID NO: 1, preferably wherein the modified retroviral RNA sequence consists of a nucleic acid sequence of SEQ ID NO: 1; and

(b) the F protein comprises a first subunit which comprises or consists of an amino acid sequence of SEQ ID NO: 14 and a second subunit which comprises or consists of an amino acid sequence of SEQ ID NO: 15.

14. The SIV vector of claim 13, wherein the vector further comprises one or more of:

(a) a p17 protein comprising or consisting of an amino acid sequence of SEQ ID NO: 2;

(b) a p24 protein comprising or consisting of an amino acid sequence of SEQ ID NO: 3;

(c) p8 protein comprising or consisting of an amino acid sequence of SEQ ID NO: 4;

(d) a protease comprising or consisting of an amino acid sequence of SEQ ID NO: 5;

(e) a p51 protein comprising or consisting of an amino acid sequence of SEQ ID NO: 6;

(f) a p15 protein comprising or consisting of an amino acid sequence of SEQ ID NO: 7;

(g) a p31 protein comprising or consisting of an amino acid sequence of SEQ ID NO: 8;

(h) a Gag protein comprising or consisting of an amino acid sequence of SEQ ID NO: 9; and/or

(i) a Pol protein comprising or consisting of an amino acid sequence of SEQ ID NO: 10;

wherein optionally the vector comprises each of (a) to (g).

15. A method of producing a retroviral vector as defined in any one of the preceding claims, said method comprising the following steps:

a) growing cells in suspension;
b) transfecting the cells with one or more plasmids;
c) adding a nuclease;
d) harvesting the lentivirus;
e) adding trypsin or an enzyme with the same cleavage specificity; and
f) purification.

16. The method of claim 15, wherein:

a. steps (a)-(f) are carried out sequentially;

b. the cells are HEK293T or 293T/17 cells;

c. the addition of the nuclease is at the pre-harvest stage;

d. the addition of trypsin or enzyme with the same cleavage specificity is at the post-harvest stage; and/or

e. the purification step comprises a chromatography step.

17. A composition comprising a retroviral vector as defined in any one of claims 1 to 14 and a pharmaceutically acceptable excipient or diluent, optionally the composition is formulated to be administered to the lungs; optionally wherein the composition is formulated to be administered by intratracheal or intranasal instillation, aerosol delivery, intravenous injection, direct injection into the lungs.

18. A retroviral vector as defined in any one of claims 1 to 14 for use in a method of treatment.

19. The retroviral vector for use of claim 18, wherein the disease to be treated is a lung disease, preferably cystic fibrosis.

20. Use of a retroviral vector as defined in any one of claims 1 to 14, in the manufacture of a medicament for the treatment of disease, wherein the disease to be treated is a lung disease, preferably cystic fibrosis.