-a second intein nucleotide sequence coding for a C-Intein, said sequence being located at the 5’ end of CDS2;

wherein when the first vector and the second vector are inserted in a cell, the protein product of the coding sequence is produced by protein splicing, wherein the coding sequence encodes a protein able to correct a retinal degeneration disorder and wherein the coding sequence is the coding sequence of a gene selected from the group consisting of: ABCA4, MYO7A, CEP290, CDH23, EYS, PCDH15, CACNA1, SNRNP200, RP1, PRPF8, RP1L1, ALMS1, USH2A, GPR98, and HMCN1;

or optionally said vector system comprising:

a’) a first vector comprising:

- said first portion of said coding sequence (CDS1),

-a first intein nucleotide sequence coding for a first N-Intein, said sequence being located at the 3’ end of CDS1; and

b’) a second vector comprising:

- said second portion of said coding sequence (CDS2),

-a second intein nucleotide sequence coding for a first C-Intein, said sequence being located at the 5’ end of CDS2;

-a third intein nucleotide sequence coding for a second N-Intein, said sequence being located at the 3’ end of CDS2; and

c') a third vector comprising:

-said third portion of said coding sequence (CDS3)

-a fourth intein nucleotide sequence coding for a second C-Intein, said sequence being located at the 5’ end of CDS3

wherein the first intein nucleotide sequence is different from the third intein nucleotide sequence when present and the second intein sequence is different from the fourth intein nucleotide sequence when present, wherein when the first vector, the second vector, and the third vector when present are inserted in a cell, the protein product of the coding sequence is produced by protein trans-splicing, and wherein the coding sequence encodes a protein able to correct a retinal degeneration disorder, wherein the coding sequence encodes a protein able to correct a retinal degeneration disorder and wherein the coding sequence is the coding sequence of a gene selected from the group consisting of: ABCA4, MYO7A, CEP290, CDH23, EYS, PCDH15, CACNA1, SNRNP200, RP1, PRPF8, RP1L1, ALMS1, USH2A, GPR98, and HMCN1.

- a fourth intein nucleotide sequence coding for a second C-Intein;
- the third portion of the coding sequence (CDS3'); and
- a 3'-inverted terminal repeat (3'-ITR) sequence.

Preferably said first, second and third vector are independently a viral vector, preferably an adeno viral vector or adeno-associated viral (AAV) vector, preferably said first, second and third adeno-associated viral (AAV) vectors are selected from the same or different AAV serotypes, preferably the serotype is selected from the serotype 2, the serotype 8, the serotype 5, the serotype 7 or the serotype 9, serotype 7m8, serotype sh10; serotype 2(quad Y-F).

In one aspect, the present disclosure also provides a host cell transformed with the vector system as defined above.

Preferably the vector system or the host cell are for medical use, preferably for use in gene therapy, preferably for use in the treatment and/or prevention of a pathology or disease characterized by a retinal degeneration, a metabolic disorder, a blood disorder, a neurodegenerative disorder, hearing loss, channelopathy, lung disease, myopathy, heart disease, muscular dystrophy. In one aspect, the present disclosure provides a use of the vector system or the host cell as disclosed herein for the manufacture of a medicament for the treatment and/or prevention of a pathology or disease characterized by a retinal degeneration.

Preferably the retinal degeneration is inherited, preferably the pathology or disease is selected from the group consisting of: retinitis pigmentosa (RP), Leber congenital amaurosis (LCA), Stargardt disease (STGD), Usher disease (USH), Alstrom syndrome, congenital stationary night blindness (CSNB), macular dystrophy, occult macular dystrophy, a disease caused by a mutation in the *ABCA4* gene.

Preferably the vector system or the host cell is for use in the prevention and/or treatment of Duchenne muscular dystrophy, cystic fibrosis, hemophilia A, Wilson disease, Phenylketonuria, dysferlinopathies, Rett's syndrome, Polycystic kidney disease, Niemann-Pick type C, Huntington's disease.

In one aspect, the present disclosure also provides a pharmaceutical composition comprising the vector system or the host cell of the disclosure and pharmaceutically acceptable vehicle.

CLAIMS

1-A vector system to express a coding sequence in a cell, said coding sequence consisting of a first portion (CDS1), a second portion (CDS2) and optionally a third portion (CDS3), said vector system comprising:

a) a first vector comprising:

- said first portion of said coding sequence (CDS1),

-a first intein nucleotide sequence coding for a N-Intein, said sequence being located at the 3' end of CDS1; and

b) a second vector comprising:

- said second portion of said coding sequence (CDS2),

-a second intein nucleotide sequence coding for a C-Intein, said sequence being located at the 5' end of CDS2;

wherein when the first vector and the second vector are inserted in a cell, the protein product of the coding sequence is produced by protein splicing, wherein the coding sequence encodes a protein able to correct a retinal degeneration disorder and wherein the coding sequence is the coding sequence of a gene selected from the group consisting of: ABCA4, MYO7A, CEP290, CDH23, EYS, PCDH15, CACNA1, SNRNP200, RP1, PRPF8, RP1L1, ALMS1, USH2A, GPR98, and HMCN1;

or optionally said vector system comprising:

a') a first vector comprising:

- said first portion of said coding sequence (CDS1),

-a first intein nucleotide sequence coding for a first N-Intein, said sequence being located at the 3' end of CDS1; and

b') a second vector comprising:

- said second portion of said coding sequence (CDS2),

-a second intein nucleotide sequence coding for a first C-Intein, said sequence being located at the 5’ end of CDS2;

-a third intein nucleotide sequence coding for a second N-Intein, said sequence being located at the 3’ end of CDS2; and

c') a third vector comprising:

-said third portion of said coding sequence (CDS3)

-a fourth intein nucleotide sequence coding for a second C-Intein, said sequence being located at the 5’ end of CDS3;

wherein the first intein nucleotide sequence is different from the third intein nucleotide sequence when present and the second intein sequence is different from the fourth intein nucleotide sequence when present, wherein when the first vector, the second vector, and the third vector when present are inserted in a cell, the protein product of the coding sequence is produced by protein splicing, and wherein the coding sequence encodes a protein able to correct a retinal degeneration disorder and wherein the coding sequence is the coding sequence of a gene selected from the group consisting of: ABCA4, MYO7A, CEP290, CDH23, EYS, PCDH15, CACNA1, SNRNP200, RP1, PRPF8, RP1L1, ALMS1, USH2A, GPR98, and HMCN1.

2- The vector system according to claim 1, wherein the first intein, the second intein, the third intein and the fourth intein when present encodes for a split intein, preferably said split intein has a maximum length of 150 amino acids, more preferably said split intein is a DnaE or DnaB intein.

3- The vector system according to claim 1 or 2, wherein:

-the first intein nucleotide sequence encodes for an intein selected from the group consisting of: SEQ ID No 1, 3, 5, 7, 9, 11, and 13;

-the second intein nucleotide sequence encodes for an intein selected from the group consisting of: SEQ ID No 2, 4, 6, 8, 10, 12, and 14;

-the third intein nucleotide sequence when present encodes for an intein selected from the group consisting of: SEQ ID No 1, 3, 5, 7, 9, 11, and 13;

-the fourth intein nucleotide sequence when present encodes for an intein selected from the group consisting of: SEQ ID No 2, 4, 6, 8, 10, 12, and 14.

4- The vector system according to any one of the previous claims, wherein the first vector, the second vector and the third vector when present further comprise a promoter sequence operably linked to the 5'end portion of said first portion of the coding sequence (CDS1) or of said second portion of the coding sequence (CDS2) or of said third portion of the coding sequence (CDS3).

5- The vector system according to any one of the previous claims, wherein the first vector, the second vector and the third vector further comprise a 5'-terminal repeat (5'-TR) nucleotide sequence and a 3'-terminal repeat (3'-TR) nucleotide sequence, preferably the 5'-TR is a 5'-inverted terminal repeat (5'-ITR) nucleotide sequence and the 3'-TR is a 3'-inverted terminal repeat (3'-ITR) nucleotide sequence.

6- The vector system according to any one of the previous claims, wherein the first vector, the second vector and the third vector further comprise a poly-adenylation signal nucleotide sequence and/or wherein at least one of the first vector or the second vector or the third vector further comprises a nucleotide sequence coding for a degradation signal.

7- The vector system according to claim 6 wherein the degradation signal is selected from the group consisting of CL1, PB29, SMN, CIITA, ODc, and ecDHFR.

8- The vector system according to any one of the previous claims, wherein the coding sequence is split into the first portion, the second portion and optionally the third portion, at a position consisting of a nucleophile amino acid which does not fall within a structural domain or a functional domain of the encoded protein product, wherein the nucleophile amino acid is selected from serine, threonine, or cysteine.

9- The vector system according to any one of previous claims, wherein at least one of the first vector, the second vector and the third vector when present further comprises at least one enhancer or regulatory nucleotide sequence, operably linked to the coding sequence.

10- The vector system according to any one of the previous claims comprising:

a) a first vector comprising in a 5’-3’ direction:

- a 5’-inverted terminal repeat (5’-ITR) sequence;

- a promoter sequence;

- a 5’ end portion of a coding sequence (CDS1), said 5’end portion being operably linked to and under control of said promoter;

- a first intein nucleotide sequence coding for a N-Intein; and

- a 3’-inverted terminal repeat (3’-ITR) sequence; and

b) a second vector comprising in a 5’-3’ direction:

- a 5’-inverted terminal repeat (5’-ITR) sequence;

- a promoter sequence;

- a second intein nucleotide sequence coding for a C-Intein;

- a 3’end portion of the coding sequence (CDS2); and

- a 3’-inverted terminal repeat (3’-ITR) sequence;

or optionally comprising:

a’) a first vector comprising in a 5’-3’ direction:

- a 5’-inverted terminal repeat (5’-ITR) sequence;

- a promoter sequence;

- a 5’ end portion of a coding sequence (CDS1’), said 5’end portion being operably linked to and under control of said promoter;

- a first intein nucleotide sequence coding for a first N-Intein ; and

- a 3’-inverted terminal repeat (3’-ITR) sequence; and

b') a second vector comprising in a 5'-3' direction:

- a 5'-inverted terminal repeat (5'-ITR) sequence;

- a promoter sequence;

- a second intein nucleotide sequence coding for a first C-Intein;

- the second portion of the coding sequence (CDS2'); and

- a third intein nucleotide sequence coding for a second N-intein;

- a 3'-inverted terminal repeat (3'-ITR) sequence; and

c') a third vector comprising in a 5'-3' direction:

- a 5'-inverted terminal repeat (5'-ITR) sequence;

- a promoter sequence;

- a fourth intein nucleotide sequence coding for a second C-Intein;

- the third portion of the coding sequence (CDS3'); and

- a 3'-inverted terminal repeat (3'-ITR) sequence.

11. The vector system according to any one of the previous claims wherein the coding sequence encodes the ABCA4 gene, preferably, said coding sequence is split at a nucleotide corresponding to aa Cys1150, Ser1168 or Ser 1090 of the ABCA4 protein, and a split intein is inserted at the split point or the coding sequence encodes the CEP290 gene, preferably, said coding sequence is split at a nucleotide corresponding to aa Cys1076 or Ser1275 of the CEP290 protein, preferably, the coding sequence encoding the CEP290 gene is split at a nucleotide sequence corresponding to aa Cys 929 and 1474 or Ser 453 and Cys 1474 of said CEP290 protein, and two split inteins are inserted at the split points.

12- The vector system according to any one of the previous claims wherein said first, second and third vector when present are independently a viral vector, preferably an adeno viral vector or adeno-associated viral (AAV) vector, preferably said first, second and third adeno-associated viral (AAV) vectors are selected from the same or different AAV serotypes,

preferably the serotype is selected from the serotype 2, the serotype 8, the serotype 5, the serotype 7 or the serotype 9, serotype 7m8, serotype sh10; serotype 2(quad Y-F).

13- A host cell transformed with the vector system according to any one of the previous claims.

14- The vector system according to any one of claims 1 to 12 or the host cell according to claim 13 for use in therapy.

15- Use of the vector system according to any one of claims 1 to 12 or the host cell according to claim 13 for the manufacture of a medicament for the treatment and/or prevention of a pathology or disease characterized by a retinal degeneration.

16- The use according to claim 15 wherein the retinal degeneration is inherited, preferably the pathology or disease is selected from the group consisting of: retinitis pigmentosa (RP), Leber congenital amaurosis (LCA), Stargardt disease (STGD), Usher disease (USH), Alstrom syndrome, congenital stationary night blindness (CSNB), macular dystrophy, occult macular dystrophy, a disease caused by a mutation in the *ABCA4* gene.

17- A pharmaceutical composition comprising the vector system according to any one of claims 1 to 12 or the host cell according to claim 13 and pharmaceutically acceptable vehicle.