

the detailed description of the invention can be used to determine whether a capsid can successfully transduce a cell.

SEQ ID NO: 3 is generated by cloning a 146 amino acid region encompassing the AAV8 VP1
5 region upstream of the VP2 and VP3 domains of the AAV3B capsid. SEQ ID NO: 4 is generated by cloning the AAV5 VP1 region upstream of the AAV3B VP2 and VP3 regions. Further details of AAV serotypes and capsid proteins is provided below.

A second aspect of the invention provides an AAV capsid comprising the AAV capsid protein
10 described above. An AAV capsid is a protein shell made up of VP1, VP2 and VP3 proteins and which encapsidates (or encloses) the genetic material of the virus.

In a third aspect, there is provided a viral particle comprising the AAV capsid protein described above. The viral particle comprises the AAV capsid and the genetic material of the
15 virus. In a fourth aspect, there is provided a nucleotide sequence which encodes for the capsid protein described above.

In another aspect, is provided a recombinant AAV vector, comprising the capsid protein as disclosed herein. In one example, there is provided a recombinant AAV (rAAV) vector
20 comprising a nucleotide sequence which encodes for the amino acid sequence described above. This means that the vector contains a nucleotide sequence encoding for a functional capsid protein.

Preferably the vector further comprises a promoter such that the nucleotide sequence is
25 expressible. Preferably the vector comprises the AAV2 p40 viral promoter, which is constitutionally active in most mammalian cell types.

Accordingly, the present invention provides gene delivery vectors based on adeno-associated virus (AAV), which normally infects humans (e.g., serotypes 1, 2, 3A, 3B, 4, 5, and 6) or
30 primates (e.g., serotypes 1 and 4). Further information on this virus is described in Kenneth I. Berns, "Parvoviridae: The Viruses and Their Replication," Chapter 69 in Fields Virology (3d Ed. 1996).

The genomic organization of all known AAV serotypes is very similar. The genome of AAV
35 is a linear, single-stranded DNA molecule that is less than about 5,000 nucleotides (nt) in length. Inverted terminal repeats (ITRs) flank the unique coding nucleotide sequences for the

The vector may comprise other elements to allow the functional therapeutic protein to be expressed. Such elements are well known to a person skilled in the art.

Preferably, the nucleic acids and amino acid sequences described above are isolated.

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It would be well with the capabilities of a skilled person to produce the nucleic acid molecules and amino acid sequences described above. This could be done, for example, using chemical synthesis of a given sequence.

10 The invention also relates to a method of transferring a nucleic acid of interest into a mammal comprising introducing a recombinant AAV vector into a mammal, the recombinant AAV vector comprising a gene of interest which is encapsidated into a capsid comprising the capsid protein described above.

15 In one aspect, the invention also provides a host cell comprising the capsid protein described above or the nucleotide sequence described above.

As used herein, the term "host" refers to organisms and/or cells which harbour a protein or a vector of the invention, as well as organisms and/or cells that are suitable for use in
20 expressing a recombinant gene or protein. It is not intended that the present invention be limited to any particular type of cell or organism. Indeed, it is contemplated that any suitable organism and/or cell will find use in the present invention as a host. A host cell may be in the form of a single cell, a population of similar or different cells, for example in the form of a culture (such as a liquid culture or a culture on a solid substrate), an organism or part thereof.

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A host cell according to the invention may permit the expression of a therapeutic nucleic acid molecule. Thus, the host cell may be, for example, a bacterial, a yeast, an insect or a mammalian cell.

30 In addition, the invention provides a transgenic animal comprising cells comprising the capsid protein having described above or the nucleotide sequence described above. Preferably the animal is a non-human mammal, especially a primate. Alternatively, the animal may be a rodent, especially a mouse; or may be canine, feline, ovine or porcine.

In one aspect, the invention provides a pharmaceutical composition comprising the viral particle as disclosed herein or the AAV vector as disclosed herein, and one or more pharmaceutically acceptable excipients. In one example, the invention provides a pharmaceutical composition comprising the capsid protein of the present invention or a
5 nucleotide sequence of the invention and one or more pharmaceutically acceptable excipients. The one or more excipients include carriers, diluents and/or other medicinal agents, pharmaceutical agents or adjuvants, etc.

The higher levels of gene transfer achieved with the sequences of the present invention
10 represents an advance beyond the current state of the art. An improvement in potency has been observed which will permit gene transfer using lower vector doses, thus improving safety (especially reducing liver toxicity which is dose dependent) and at a lower cost. Accordingly the sequences and vector of the present invention may have a clinical applicability to disorders such as congenital FVII deficiency, Gaucher's disease, OTC
15 deficiency, Fabry's disease, glycogen storage diseases, α -1-antitrypsin deficiency, progressive familial intrahepatic cholestasis, Wilson's disease, Crigler Najjar syndrome and hepatocellular carcinoma amongst others.

Accordingly, the invention may provide a method of treating one or more of the diseases
20 listed above comprising administering a therapeutically effective amount of a vector as described above to a patient suffering from said disease. Preferably, the patient is human.

When said disease is "treated" in the above method, this means that one or more symptoms of said disease are ameliorated. It does not mean that the symptoms of said disease are
25 completely remedied so that they are no longer present in the patient, although in some methods, this may be the case. The method of treating results in one or more of the symptoms of said disease being less severe than before treatment.

A "therapeutically effective amount" refers to an amount effective, at dosages and for periods
30 of time necessary, to achieve the desired therapeutic result.

In one aspect, the invention provides a viral particle as disclosed herein or the AAV vector as disclosed herein for use in therapy. Further, the invention may provide the capsid protein as described above, or a vector as described above for use in therapy, preferably for one of the
35 afore-mentioned diseases.

CLAIMS

1. An AAV capsid protein having an amino acid sequence which:
 - (i) has the sequence of SEQ ID NO: 3; or
 - (ii) has at least 99% identity to the sequence of SEQ ID NO: 3 and is a hybrid
- 5 capsid comprising regions of the AAV3B and AAV8 capsids.
2. The AAV capsid protein of claim 1, wherein the amino acid sequence has at least 99.5% identity to the sequence of SEQ ID NO: 3.
- 10 3. The AAV capsid protein of claim 1 or claim 2, wherein the amino acid sequence has the sequence of SEQ ID NO: 3.
4. An AAV capsid comprising the capsid protein of any one of claims 1 to 3.
- 15 5. A viral particle comprising the capsid protein of any one of claims 1 to 3.
6. A nucleotide sequence which encodes for the capsid protein of any one of claims 1 to 3.
- 20 7. A host cell comprising the capsid protein of any one of claims 1 to 4 or the nucleotide sequence of claim 6.
8. A recombinant AAV vector, comprising the capsid protein of any one of claims 1 to 3.
- 25 9. A pharmaceutical composition comprising the viral particle of claim 5 or the AAV vector of claim 8, and one or more pharmaceutically acceptable excipients.
10. The viral particle of claim 5 or the AAV vector of claim 8 for use in therapy.