There are significant challenges to overcome in developing a successful gene therapy for AS. The first is that the COL4A5, COL4A3 and COL4A4 proteins are 1685, 1670 and 1690 amino acids each, rendering them challenging for transport by an adeno-associated virus (AAV) vector, due to limited AAV cargo capacity. The second significant challenge is to successfully deliver the gene therapy to podocyte cells in the glomerulus of the kidney, which produce collagen IV in the glomerular basement membrane.

The present invention aims to provide a novel gene therapy vector that can efficiently deliver a COL4A3, COL4A4 or COL4A5 transgene to podocytes and thereby provide a therapy for the treatment of Alport syndrome.

SUMMARY

The present disclosure provides a viral vector, wherein the viral vector comprises a COL4A3, COL4A4 or COL4A5 transgene. The viral vector can be used to target podocytes within the glomerulus of the kidney in order to treat Alport syndrome.

Without being bound by theory, the present inventors believe that podocytes offer a highly tractable target for gene therapy approaches in kidney disease and that by targeting COL4A3, COL4A4 or COL4A5 to podocytes the collagen IV α345 network of the glomerular basement membrane can be changed and at least partially normalised.

In one aspect, the present disclosure provides a viral vector, wherein the viral vector comprises a COL4A3, COL4A4 or COL4A5 transgene, wherein the viral vector comprises a podocyte-specific promoter. In one example, present disclosure provides a viral vector, wherein the viral vector comprises a COL4A3, COL4A4 or COL4A5 transgene.

The COL4A3 transgene may encode a COL4A3 polypeptide which comprises or consists of the polypeptide sequence having at least 70% identity to SEQ ID NO: 1, or a fragment thereof; the COL4A4 transgene may encode a COL4A4 polypeptide which comprises or consists of the polypeptide sequence having at least 70% identity to SEQ ID NO: 2, or a fragment thereof; and/or the COL4A5 transgene may encode a COL4A5 polypeptide which comprises or consists of the polypeptide sequence having at least 70% identity to SEQ ID NO: 3, or a fragment thereof. In some examples, the COL4A3 transgene encodes a full-length COL4A3 polypeptide, the COL4A4 transgene encodes a full-length COL4A4 polypeptide; and/or the COL4A5 transgene encodes a full-length COL4A5

In one example, the present invention provides a viral vector gene therapy, wherein the viral vector comprises a COL4A3, COL4A4 or COL4A5 transgene.

In preferred examples, the viral vector is a viral vector according to the present disclosure.

In one aspect, the present disclosure provides a viral vector gene therapy product, wherein the gene therapy product comprises: a first viral vector comprising at least a portion of a COL4A3, COL4A4 or COL4A5 transgene; and a second viral vector comprising at least a portion of a corresponding COL4A3, COL4A4 or COL4A5 transgene. In one example, the present disclosure provides a viral vector gene therapy, wherein the gene therapy comprises:

a first viral vector comprising at least a portion of a COL4A3, COL4A4 or COL4A5 transgene; and

a second viral vector comprising at least a portion of a corresponding COL4A3, COL4A4 or COL4A5 transgene.

In preferred examples, the first viral vector is a viral vector according to the present disclosure, and/or the second viral vector is a viral vector according to the present disclosure.

In one aspect, the present disclosure provides a use of a viral vector or viral vector gene therapy product as disclosed herein in the manufacture of a medicament for treating or preventing Alport Syndrome. In one example, the present disclosure provides a viral vector or viral vector gene therapy according to the present invention, for use in treating or preventing Alport Syndrome.

Suitably, the viral vector or viral vector gene therapy is administered to a human patient. In some examples, the viral vector or viral vector gene therapy is administered systemically. In some examples, the viral vector or viral vector gene therapy is administered by intravenous injection. In some examples, the viral vector or viral vector gene therapy is administered by injection into the renal artery.

Viral vectors

Adeno-associated viral (AAV) vectors

The viral vector may be an adeno-associated virus (AAV) and suitable AAV vector serotypes include 2/9, LK03 and 3B.

The viral vector may be in the form of an AAV vector particle.

CLAIMS

1. A viral vector, wherein the viral vector comprises a COL4A3, COL4A4 or COL4A5 transgene, wherein the viral vector comprises a podocyte-specific promoter.

2. The viral vector according to claim 1, wherein:

(i) the COL4A3 transgene encodes a COL4A3 polypeptide which comprises or consists of a polypeptide sequence having at least 90% identity to SEQ ID NO: 1, or a fragment thereof;
(ii) the COL4A4 transgene encodes a COL4A4 polypeptide which comprises or consists of a polypeptide sequence having at least 90% identity to SEQ ID NO: 2, or a fragment thereof; and/or
(iii) the COL4A5 transgene encodes a COL4A5 polypeptide which comprises or consists of a polypeptide sequence having at least 90% identity to SEQ ID NO: 3, or a fragment thereof.

3. The viral vector according to claim 1 or 2, wherein: (i) the COL4A3 transgene encodes a full-length COL4A3 polypeptide, (ii) the COL4A4 transgene encodes a full-length COL4A4 polypeptide; and/or (iii) the COL4A5 transgene encodes a full-length COL4A5 polypeptide.

4. The viral vector according to any of the preceding claims, wherein the podocyte-specific promoter is minimal nephrin promoter NPHS1 or podocin promoter NPHS2, preferably wherein the podocyte-specific promoter is minimal nephrin promoter NPHS1.

5. The viral vector according to claim 4, wherein the minimal nephrin promoter NPHS1 comprises or consists of the nucleotide sequence shown as SEQ ID NO: 10, or a variant which is at least 90% identical to SEQ ID NO: 10; or
the minimal nephrin promoter NPHS1 comprises the nucleotide sequence of SEQ ID NO. 12, or a functional variant which is at least 90% identical thereto.

6. The viral vector according to any of the preceding claims, wherein the viral vector is an adeno-associated virus (AAV) vector.

7. The viral vector according to claim 6, wherein the AAV vector is encapsidated in an AAV vector particle.

8. The viral vector according to claim 7, wherein the AAV vector particle is a podocyte-specific AAV vector.

9. The viral vector according to claim 7 or 8, wherein the AAV vector particle is AAV serotype 2/9, LK03 or 3B.

10. The viral vector according to any of the preceding claims, wherein the COL4A3, COL4A4 or COL4A5 transgene is a mini-gene.

11. The viral vector according to any of the preceding claims, wherein the viral vector additionally comprises a Woodchuck hepatitis post-transcriptional regulatory element (WPRE).

12. The viral vector according to any of claims 1 to 10, wherein the viral vector does not comprise Woodchuck hepatitis post-transcriptional regulatory element (WPRE).

13. The viral vector according to any of the preceding claims, wherein the COL4A3, COL4A4 or COL4A5 transgene is human and/or comprises a hemagglutinin (HA) tag.

14. The viral vector according to any of the preceding claims, wherein the viral vector additionally comprises a Kozak sequence between the promoter and the COL4A3, COL4A4 or COL4A5 transgene.

15. The viral vector according to any of the preceding claims, wherein the viral vector additionally comprises a polyadenylation signal such as bovine growth hormone (bGH) polyadenylation signal or an early SV40 polyadenylation signal.

16. The viral vector according to claim 15, wherein the polyadenylation signal is an early SV40 polyadenylation signal.

17. A viral vector gene therapy product, wherein the gene therapy product comprises:

a first viral vector comprising at least a portion of a COL4A3, COL4A4 or COL4A5 transgene; and

a second viral vector comprising at least a portion of a corresponding COL4A3, COL4A4 or COL4A5 transgene.

18. The viral vector gene therapy product according to claim 17, wherein the first viral vector is a viral vector as defined in any of claims 1 to 16 and/or the second viral vector is a viral vector as defined in any of claims 1 to 16.

19. Use of the viral vector or viral vector gene therapy product according to any of the preceding claims in the manufacture of a medicament for treating or preventing Alport Syndrome.

20. The use according to claim 19, wherein the viral vector or viral vector gene therapy product is to be administered to a human patient.

21. The use according to claims 19 or 20, wherein the viral vector or viral vector gene therapy product is to be administered systemically.

22. The use according to any of claims 19 to 21, wherein the viral vector or viral vector gene therapy product is to be administered by intravenous injection.

23. The use according to any of claims 19 or 20, wherein the viral vector or viral vector gene therapy product is to be administered by injection into the renal artery.