

CLAIMS:

1. A combination regimen for treating a patient with immunoglobulin G (IgG) neutralizing antibodies to a selected AAV capsid or an AAV capsid serologically cross-reactive to the selected capsid, the regimen comprising (a) administering an AAV viral vector comprising the selected AAV capsid and a vector genome comprising a nucleic acid sequence encoding a gene product operably linked to regulatory sequences which direct expression thereof in a target cell, and (b) co-administering a ligand which specifically prevents binding between human neonatal Fc receptor (FcRn) and the neutralizing antibodies without interfering with albumin binding to FcRn.
2. The combination regimen according to claim 1, wherein the ligand is selected from a peptide, protein, an RNAi sequence, or a small molecule.
3. The combination regimen according to claim 1 or 2, wherein the ligand is a monoclonal antibody, an immunoadhesin, a camelid antibody, a Fab fragment, an Fv fragment, or an scFv fragment directed against FcRn.
4. The combination regimen according to any one of claims 1 to 3, wherein the ligand is a monoclonal antibody selected from nipocalimab (M281), rozanolixizumab; IMVT-1401, RVT-1401, HL161, HBM916, efgartigimod, orilanolimab (SYNT001), SYNT002, ABY-039, DX-2507, derivatives or combinations thereof.
5. The combination regimen according to any one of claims 1 to 4, wherein the ligand is nipocalimab (M281) or an immunoglobulin construct which comprises three or more CDRs thereof selected from:
 - (a) heavy chain CDRs of (i) CDR H1, SEQ ID NO: 16 or a sequence at least 99% identical thereto, (ii) CDR H2, SEQ ID NO: 18 or a sequence at least 99% identical thereto, and (iii) CDR H3, SEQ ID NO: 20 or a sequence at least 99% identical thereto; or
 - (b) light chain CDRs of: CDR L1, SEQ ID NO: 10 or a sequence at least 99% identical thereto, CDR L2, SEQ ID NO: 12 or a sequence at least 99% identical thereto, CDR L3, SEQ ID NO: 14, or a sequence at least 99% identical thereto.

6. The combination regimen according to claim 5, wherein nipocalimab or the immunoglobulin construct comprises:
- (a) heavy chain CDRs of (i) CDR H1, SEQ ID NO: 16, (ii) CDR H2, SEQ ID NO: 18, and (iii) CDR H3, SEQ ID NO: 20; or
 - (b) light chain CDRs of: CDR L1, SEQ ID NO: 10, CDR L2, SEQ ID NO: 12, CDR L3, SEQ ID NO: 14.
7. The combination regimen according to any one of claims 1 to 6, wherein the ligand is expressed in vivo following delivery of a vector comprising sequences encoding the ligand operably linked to regulatory sequences which direct expression of the ligand.
8. The combination regimen according to any one of claims 1 to 7, wherein the rAAV encoding the gene product has a capsid selected from AAV1, AAV2, AAV3, AAV5, AAV7, AAV8, AAV9, AAVrh10, AAVrh91, AAVhu37, or AAVhu68.
9. The combination regimen according to any one of claims 1 to 8, wherein prior to delivery of the combination regimen, the patient has a neutralizing titer greater than 1:5 against the rAAV capsid or a serologically cross-reactive capsid as determined in an in vitro assay.
10. The combination regimen according to any one of claims 1 to 9, wherein the ligand is delivered one to seven days prior to delivery of the rAAV.
11. The combination regimen according to any one of claims 1 to 10, wherein the ligand is delivered daily.
12. The combination regimen according to any one of claims 1 to 11, wherein the ligand is delivered on the same day as when the rAAV is delivered.
13. The combination regimen according to any one of claims 1 to 9, wherein the ligand is delivered for one day to four weeks and/or for four weeks to 6 months post-rAAV delivery.

14. The combination regimen according to any one of claims 1 to 14, wherein the ligand is delivered orally.
15. The combination regimen according to any one of claims 1 to 14, wherein the rAAV is delivered systemically, optionally via intraperitoneal, intravenous, intramuscular, or intranasally, or intrathecally.
16. The combination regimen according to any one of claims 1 to 15, wherein the patient has not previously received gene therapy treatment or gene delivery using an AAV prior to delivery of the viral vector in combination with the inhibitory ligand such that the patient's pre-existing neutralizing antibodies are a result of wild-type viral vector infection.
17. The combination regimen according to any one of claims 1 to 16, wherein the regimen further comprises co-administering one or more of: (a) a steroid or combination of steroids; and/or (b) an IgG-cleaving enzyme; and (c) an inhibitor of Fc-IgE binding; (d) an inhibitor of Fc-IgM binding; (e) an inhibitor of Fc-IgA binding; and/or (f) gamma interferon.
18. Use of an anti-FcRn antibody in the manufacture of a medicament useful in a combination regimen according to any one of claims 1 to 17 for treating a patient in need thereof with an effective amounts of the gene product.
19. Use of an rAAV vector comprising a transgene for delivery to a cell in the manufacture of a medicament useful in a combination regimen comprising co-administration of the rAAV vector with an anti-FcRn antibody according to any one of claims 1 to 17.
20. A method for increasing the patient population for which rAAV-mediated gene therapy is effective,

said method comprising co-administering to a patient from a population having a neutralizing antibody titer to a selected AAV viral capsid or a serologically cross-reactive capsid which prevents effective transfer and expression levels of the transgene product:

(a) a recombinant rAAV having a selected AAV capsid and a vector genome packaged in the selected capsid; and

(b) a ligand which specifically binds a neonatal Fc receptor (FcRn) prior to delivery of the gene therapy vector without substantially interfering with FcRn-albumin binding,

wherein the ligand blocks binding of the FcRn to immunoglobulin G (IgG), and permits effective amounts of the gene therapy product to be expressed in the patient.

21. The method according to claim 20, wherein the immunoglobulin construct is selected from a monoclonal antibody, an immunoadhesin, a camelid antibody, a Fab fragment, an Fv fragment, or an scFv fragment.

22. The method according to claim 20, wherein the rAAV is delivered systemically.

23. The method according to claim 20, wherein the rAAV is delivered intravenously, intraperitoneally, intranasally, or via inhalation.

24. The method according to claim 20, wherein the rAAV has a capsid selected from AAV1, AAV2, AAV3, AAV5, AAV7, AAV8, AAV9, AAVrh10, AAVrh91, AAVhu37, AAVhu68.

25. The method according to claim 20, wherein the immunoglobulin construct is a monoclonal antibody nipocalimab (M281) or an immunoglobulin construct which comprises three or more CDRs thereof.

26. The method according to claim 25, wherein the immunoglobulin construct comprises:

(a) heavy chain CDRs of (i) CDR H1, SEQ ID NO: 16 or a sequence at least 99% identical thereto, (ii) CDR H2, SEQ ID NO: 18 or a sequence at least 99% identical thereto, and (iii) CDR H3, SEQ ID NO: 20 or a sequence at least 99% identical thereto is selected; or

(b) light chain CDRs of: CDR L1, SEQ ID NO: 10 or a sequence at least 99% identical thereto, CDR L2, SEQ ID NO:12 or a sequence at least 99% identical thereto, CDR L3, SEQ ID NO: 14, or a sequence at least 99% identical thereto.

27. The method according to claim 20, wherein the immunoglobulin construct is selected from rozanolixizumab (UCB7665), IMVT-1401, RVT-1401, HL161, HBM916, ARGX-113 (efgartigimod), SYNT001, SYNT002, ABY-039, or DX-2507, or a derivative of the immunoglobulin construct, or a combination of the immunoglobulin constructs and/or derivatives thereof.

28. The method according to claim 20, wherein the immunoglobulin construct is delivered one to seven days prior to delivery of the rAAV.

29. The method according to claim 20, wherein the immunoglobulin construct is delivered daily.

30. The method according to claim 20, wherein the immunoglobulin construct is delivered on the same day as the rAAV is delivered.

31. The method according to claim 20, wherein the immunoglobulin construct is delivered at least one day to four weeks post-rAAV delivery.

32. The method according to claim 30, wherein the immunoglobulin construct is delivered for four weeks to 6 months post-rAAV delivery.

33. The method according to claim 20, wherein the immunoglobulin construct is delivered via a different route of than the rAAV is delivered.

34. The method according to claim 20, wherein the immunoglobulin construct is delivered orally.

35. The method according to claim 20, wherein the patient was predetermined to have a neutralizing titer greater than 1:5 as determined in an in vitro assay.

36. The method according to claim 20, wherein the method is part of a regimen which further comprises co-administering one or more of: (a) a steroid or combination of steroids and/or (b) an IgG-cleaving enzyme, (c) an inhibitor of Fc-IgE binding; (d) an inhibitor of Fc-IgM binding; (e) an inhibitor of Fc-IgA binding; and/or (f) gamma interferon.