[0005] Despite many years of research into the potential of using human intravenous immunoglobulin (IV Ig) and monoclonal antibodies (mAb) as therapeutics, progress has been hampered by concerns and risks of, among others, antibody-dependent enhancements (ADE) or antibody-dependent cell-mediated cytotoxicity (ADCC), as well as technical barriers to humanizing monoclonal antibodies and risk of other pathogen spreading through the use of human intravenous immunoglobulin.

[0006] There are currently no commercial vaccines or therapeutics available capable of preventing or treating the diseases disclosed herein. Maintaining good personal hygiene and quarantined of infected individual have been the only measures taken by the public health sector. Thus, there is an unmet need for systems, compositions and methods of detecting and treating the viral diseases disclosed herein.

SUMMARY

[0007] In one aspect, the present disclosure refers to a molecular system comprising (a) an RNA-guided RNA-targeting effector protein, and (b) one or more guide RNA molecule (gRNA); wherein each of the one or more guide RNAs comprise a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or 100% identical to one of the sequences set forth in SEQ ID NO: 1 to 6.

[0008] In another aspect, the present disclosure refers to a molecular system comprising (a) an RNA-guided RNA-targeting effector protein, and (b) a collection of at least 4 different guide RNA molecules (gRNAs); wherein at least 4 of the gRNAs in said collection comprise a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or 100% identical to one of the sequences set forth in SEQ ID NO: 1 to 6.

[0009] In a further aspect, the present disclosure refers to a use of the molecular system as disclosed herein in the manufacture of a medicament for treating a disease associated with or caused by the infection, propagation and/or replication of an RNA virus. In yet another aspect, the present disclosure refers to a use of a molecular system in the manufacture of a medicament for treating, preventing, suppressing, and/or alleviating a disease associated with or caused by infection, propagation and/or replication of an RNA virus in a subject; wherein the molecular system comprises (a) an RNA-guided RNA-targeting effector protein and/or a polynucleic acid encoding said effector protein, and (b) one or more gRNAs and/or one or more polynucleic acids encoding said one or more gRNAs; wherein each

of the one or more gRNAs comprises a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95% or 100% identical to one of the sequences set forth in SEQ ID NO: 1-6.

[0010] In a further aspect, the present disclosure refers to a use of a molecular system in the manufacture of a medicament for treating, preventing, suppressing, and/or alleviating a disease associated with or caused by infection, propagation and/or replication of an RNA virus in a subject, wherein the

molecular system comprises (a) an RNA-guided RNA-targeting effector protein and/or a polynucleic acid encoding said effector protein, and (b) a collection of at least 4 different gRNAs and/or one or more polynucleic acids encoding said collection of gRNAs; wherein at least 4 of the gRNAs in said collection comprise a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95% or 100% identical to one of the sequences set forth in SEQ ID NO: 1-6.

[0011] In one aspect, the present disclosure refers to polynucleotides encoding the molecular system as disclosed herein.

[0012] In another aspect, the present disclosure refers to a vector encoding one or more gRNAs, wherein the one or more gRNAs encoded by said vector comprise a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or 100% identical to one of the sequences set forth in SEQ ID NO: 1-6.

[0013] In yet another aspect, the present disclosure refers to a vector encoding the molecular system as disclosed herein.

[0014] In one aspect, the present disclosure refers to a composition comprising the polynucleotide as disclosed herein, and/or the vector as disclosed herein.

[0015] In a further aspect, the present disclosure refers to a method of treating, preventing, suppressing, and/or alleviating a disease associated with or caused by pathogenesis, infection, propagation and/or replication of a virus of the Enterovirus genus in a subject, comprising administering to a subject in need thereof the polynucleotides as disclosed herein, and/or the vector as disclosed herein, and/or the composition as disclosed herein.

[0016] In one aspect, the present disclosure refers to a guide RNA molecule (gRNA), comprising a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or 100% identical to any one of the sequences set forth in SEQ ID NO: 1-6.

[0017] In another aspect, the present disclosure refers to a guide RNA molecule comprising a guide sequence as set forth in any one of SEQ NO: 1-6.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which

[0019] **Fig. 1** shows a schematic showing the design and construction of plasmid for AAV packaging of CRISPR-CasRx. Plasmid of pZac2.1-CMV-CasRx-3xHA-PolyA-U6-gRNA. Between the ITR sequences, there is a CMV promoter which drives the expression of CasRx

CLAIMS

1. A molecular system comprising (a) an RNA-guided RNA-targeting effector protein, and (b) one or more guide RNA molecule (gRNA); wherein each of the one or more guide RNAs comprise a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or 100% identical to one of the sequences set forth in SEQ ID NO: 1 to 6.

2. A molecular system comprising (a) an RNA-guided RNA-targeting effector protein, and (b) a collection of at least 4 different guide RNA molecules (gRNAs); wherein at least 4 of the gRNAs in said collection comprise a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or 100% identical to one of the sequences set forth in SEQ ID NO: 1 to 6.

3. The molecular system of claim 2, wherein at least 4 of the gRNAs in said collection comprise a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or 100% identical to one of the sequences set forth in SEQ ID NO: 1 to 4.

4. The molecular system of claim 2 or 3, wherein the collection comprises at least 6 different gRNAs, wherein 6 of the gRNAs in said collection comprise a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or 100% identical to one of the sequences set forth in SEQ ID NO: 1 to 6.

5. The molecular system of any of claims 1 to 4, wherein the RNA-guided RNA-targeting effector protein is an RNA-guided RNA-targeting Cas protein, or a modified variant thereof.

6. The molecular system of claim 5, wherein the Cas protein is selected from the group consisting of: a Cas13a, a Cas13b, a Cas13c, and a Cas13d.

7. The molecular system of claim 6, wherein the Cas13d is the Cas13d orthologue of *Ruminococcus flavefaciens* (CasRx).

8. The molecular system of claim 7, wherein the Cas protein is a CasRx; and wherein the collection comprises 6 different guide RNA molecules (gRNAs), wherein each of the gRNAs comprises a guide sequence that is set forth in SEQ ID NO: 1 to 6.

9. The molecular system of any one of claims 1 to 8 for use in therapy.

10. Use of the molecular system of any one of claims 1 to 9 in the manufacture of a medicament for treating a disease associated with or caused by the infection, propagation and/or replication of an RNA virus.

11. The use of the molecular system of claim 10, wherein the RNA virus is a virus of the Enterovirus genus.

12. The use of the molecular system according to any one of claims 10 to 11, wherein the disease is selected from the group consisting of: polio; mild respiratory illness (the common cold); hand, foot, and mouth disease (HFMD); acute hemorrhagic conjunctivitis; aseptic meningitis; myocarditis; severe neonatal sepsis-like disease; acute flaccid paralysis; acute flaccid myelitis; Bornholm disease; epidemic pleurodynia; Herpangina; and chronic fatigue syndrome.

13. The use of the molecular system according to claim 11, wherein the disease is hand, foot, and mouth disease (HFMD).

14. The use of the molecular system according to claim 13, wherein the disease is caused by an RNA virus selected from the group consisting of Enterovirus, Coxsackie virus and Parechovirus.

15. The use of the molecular system according to claim 14, wherein: i) the Enterovirus is Enterovirus 71; ii) the Coxsackie virus is selected from the group consisting of CAV16 and CAV6; and iii) the Parechovirus is selected from the group consisting of Parechovirus A, Parechovirus B, Parechovirus C, Parechovirus D, Parechovirus E, and Parechovirus F.

16. Use of a molecular system in the manufacture of a medicament for treating, preventing, suppressing, and/or alleviating a disease associated with or caused by infection,

propagation and/or replication of an RNA virus in a subject; wherein the molecular system comprises (a) an RNA-guided RNA-targeting effector protein and/or a polynucleic acid encoding said effector protein, and (b) one or more gRNAs and/or one or more polynucleic acids encoding said one or more gRNAs; wherein each of the one or more gRNAs comprises a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95% or 100% identical to one of the sequences set forth in SEQ ID NO: 1-6.

17. Use of a molecular system in the manufacture of a medicament for treating, preventing, suppressing, and/or alleviating a disease associated with or caused by infection, propagation and/or replication of an RNA virus in a subject; wherein the molecular system comprises (a) an RNA-guided RNA-targeting effector protein and/or a polynucleic acid encoding said effector protein, and (b) a collection of at least 4 different gRNAs and/or one or more polynucleic acids encoding said collection of gRNAs; wherein at least 4 of the gRNAs in said collection comprise a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95% or 100% identical to one of the sequences set forth in SEQ ID NO: 1-6.

18. The use according to claim 17, wherein at least 4 of the gRNAs in said collection comprise a guide sequence that is at least 70%, at least 80%, at least 90% at least 95%, or 100% identical to one of the sequences set forth in SEQ ID NO: 1-4.

19. The use according to claim 17 or 18, wherein collection (b) comprises at least 6 different gRNAs, wherein 6 of the gRNAs in said collection comprise a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or 100% identical to one of the sequences set forth in SEQ ID NO: 1-6.

20. The use according to any one of claims 16-19, wherein the polynucleic acid encoding said effector protein and/or the one or more polynucleic acids encoding said gRNAs are comprised in one or more vectors.

21. The use according to claim 20, wherein the vector is a viral vector.

22. The use according to claim 21, wherein the viral vector is an adenoviral vector, an Adeno-associated virus (AAV) vector, a lentiviral vector, or a retroviral vector.

23. The use according to claim 22, wherein the viral vector is an AAV vector.

24. The use according to claim 23, wherein the AAV vector is selected from the group consisting of: AAV type 1 (AAV-1), AAV type 2 (AAV-2), AAV type 3 (AAV-3), AAV type 4 (AAV-4), AAV type 5 (AAV-5), AAV type 6 (AAV-6), AAV type 7 (AAV-7), AAV type 8 (AAV-8), AAV9, AAV10, AAV11, AAV12, AAV13, rh10, AAVDJ, AAV-PHP.S, AAV-PHP.B, AAV-PHP.eB, and Anc80.

25. The use according to claim 24, wherein the AAV vector is an AAV2, or AAVDJ, or AAV1 vector.

26. The use according to any one of claims 16-25, wherein the RNA-guided RNA-targeting effector protein is an RNA-guided RNA-targeting Cas protein, or a modified variant thereof.

27. The use according to any one of claims 16-26, wherein the Cas protein is selected from the group consisting of: a Cas13a, a Cas13b, a Cas13c, and a Cas13d.

28. The use according to claim 27, wherein the Cas13d is the Cas13d orthologue of *Ruminococcus flavefaciens* (CasRx).

29. The use according to any one of claims 13 to 28, wherein the disease is caused by an RNA virus.

30. The use according to claim 29, wherein the RNA virus is an Enterovirus.

31. The use according to any of claims 16-28, wherein the disease is selected from the group consisting of: polio; mild respiratory illness (the common cold); hand, foot, and mouth disease (HFMD); acute hemorrhagic conjunctivitis; aseptic meningitis; myocarditis; severe neonatal sepsis-like disease; acute flaccid paralysis; acute flaccid myelitis; Bornholm disease; epidemic pleurodynia; Herpangina; chronic fatigue syndrome; and Diabetes mellitus type 1.

32. The use according to claim 31, wherein the disease is hand, foot, and mouth disease (HFMD).

33. The use according to claim 32 wherein the disease is HFMD caused by an RNA virus selected from the group consisting of Enterovirus, Coxsackie virus and Parechovirus.

34. The use according to any one of claims 32 and 33, wherein: i) the Enterovirus is Enterovirus 71; ii) the Coxsackie virus is selected from the group consisting of CAV16 and CAV6; and iii) the Parechovirus is selected from the group consisting of Parechovirus A, Parechovirus B, Parechovirus C, Parechovirus D, Parechovirus E, and Parechovirus F.

35. Polynucleotides encoding the molecular system of any one of claims 1-15.

36. A vector encoding one or more gRNAs, wherein the one or more gRNAs encoded by said vector comprise a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or 100% identical to one of the sequences set forth in SEQ ID NO: 1-6.

37. The vector of claim 36, wherein the vector encodes at least 4 different gRNAs, wherein each of the gRNAs comprises a guide sequence that is set forth in SEQ ID NO: 1-6.

38. The vector of claim 37, wherein the vector encodes 6 different gRNAs, wherein each of the gRNAs comprises a guide sequence that is set forth in SEQ ID NO: 1-6.

39. A vector encoding the molecular system of any one of claims 1-15.

40. The vector of any one of claims 36-39, wherein the vector is an adenoviral vector, an Adeno-associated virus (AAV) vector, a lentiviral vector, or a retroviral vector.

41. The vector of claim 40, wherein the vector is an AAV vector.

42. The vector of claim 42, wherein the vector is selected from the group consisting of: AAV type 1 (AAV-1), AAV type 2 (AAV-2), AAV type 3 (AAV-3), AAV type 4 (AAV-4), AAV type 5 (AAV-5), AAV type 6 (AAV-6), AAV type 7 (AAV-7), AAV type 8 (AAV-

8), AAV9, AAV10, AAV11, AAV12, AAV13, rh10, AAVDJ, AAV-PHP.S, AAV-PHP.B, AAV-PHP.eB, and Anc80.

43. The vector of claim 42, wherein the AAV vector is an AAV2, AAVDJ or AAV1 vector.

44. A composition comprising the polynucleotide of claim 35, and/or the vector of any one of claims 36-43.

45. The composition of claim 44, further comprising an RNA-guided RNA-targeting effector protein.

46. The composition of claim 45, wherein the RNA-guided RNA-targeting effector protein is a Cas protein selected from the group consisting of: a Cas13a, a Cas13b, a Cas13c, and a Cas13d.

47. The composition of claim 46, wherein the Cas13d is the Cas13d orthologue of *Ruminococcus flavefaciens* (CasRx).

48. The composition of any one of claims 44-47 for use in therapy.

49. Use of the polynucleotides of claim 35, and/or the vector of any one of claims 36-43, and/or the composition of any one of claims 44-47 in the manufacture of a medicament for treating, preventing, suppressing, and/or alleviating a disease associated with or caused by pathogenesis, infection, propagation and/or replication of a virus of the Enterovirus genus in a subject.

50. The use of claim 49, wherein the disease is selected from the group consisting of: polio; mild respiratory illness (the common cold); hand, foot, and mouth disease (HFMD); acute hemorrhagic conjunctivitis; aseptic meningitis; myocarditis; severe neonatal sepsis-like disease; acute flaccid paralysis; acute flaccid myelitis; Bornholm disease; epidemic pleurodynia; Herpangina; and chronic fatigue syndrome.

51. The use of claim 50, wherein the disease is Hand Foot Mouth Disease (HFMD).

52. A guide RNA molecule (gRNA), comprising a guide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or 100% identical to any one of the sequences set forth in SEQ ID NO: 1-6.

53. A guide RNA molecule comprising a guide sequence as set forth in any one of SEQ NO: 1-6.