

We claim:

1. A use of a nuclease agent or one or more nucleic acids encoding the nuclease agent and an exogenous donor nucleic acid comprising an antibody coding sequence in the manufacture of a medicament for treating a disease or effecting prophylaxis of an infectious disease in an animal having or at risk for the disease,
 - wherein the nuclease agent targets a target site in the first intron of an albumin locus in one or more liver cells in the animal,
 - wherein the antibody targets an antigen associated with the disease,
 - wherein the nuclease agent is a zinc finger nuclease (ZFN), a Transcription Activator-Like Effector Nuclease (TALEN), or a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated (Cas) protein and a guide RNA (gRNA),
 - wherein the nuclease agent cleaves the target site and the antibody coding sequence is to be inserted into the first intron of the albumin locus in the one or more liver cells in the animal to produce a modified albumin locus,
 - wherein the antibody is not a single-chain antibody,
 - wherein the antibody comprises a heavy chain and a separate light chain,
 - wherein the heavy chain coding sequence is upstream of the light chain coding sequence in the antibody coding sequence,
 - wherein the heavy chain and the light chain are linked by a T2A peptide,
 - wherein a nucleic acid encoding a furin cleavage site is included between the heavy chain coding sequence and the light chain coding sequence, and wherein the furin cleavage site is upstream of the T2A peptide,
 - wherein the heavy chain coding sequence is operably linked to an endogenous albumin secretion signal sequence in the modified albumin locus, and the antibody coding sequence comprises an exogenous secretion signal sequence upstream of the light chain coding sequence,
 - wherein the inserted antibody coding sequence is operably linked to an endogenous albumin promoter in the modified albumin locus, and
 - whereby the antibody is expressed in the animal and binds the antigen associated with the disease.

2. The use of claim 1, wherein the nuclease agent is the Cas protein and the gRNA, wherein the Cas protein is a Cas9 protein, and wherein the gRNA comprises:
 - (a) a CRISPR RNA (crRNA) that targets the target site, wherein the target site is immediately flanked by a Protospacer Adjacent Motif (PAM) sequence; and
 - (b) a trans-activating CRISPR RNA (tracrRNA).
3. The use of claim 2, wherein the at least one gRNA comprises 2'-O-methyl analogs and 3' phosphorothioate internucleotide linkages at the first three 5' and 3' terminal RNA residues.
4. The use of any preceding claim, wherein the antibody coding sequence is to be inserted via non-homologous end joining.
5. The use of any one of claims 1-3, wherein the antibody coding sequence is to be inserted via homology-directed repair.
6. The use of any one of claims 1-4, wherein the exogenous donor nucleic acid does not comprise homology arms.
7. The use of any preceding claim, wherein the exogenous donor nucleic acid is single-stranded.
8. The use of any one of claims 1-6, wherein the exogenous donor nucleic acid is double-stranded.
9. The use of any preceding claim, wherein the antibody coding sequence in the exogenous donor nucleic acid is flanked on each side by the target site for the nuclease agent.
10. The use of claim 9, wherein the target site in the safe harbor locus is no longer present if the antibody coding sequence is inserted into the safe harbor locus in the correct orientation but it is reformed if the antibody coding sequence is inserted into the safe harbor locus in the opposite orientation.

11. The use of claim 9 or 10, wherein the exogenous donor nucleic acid is in an adeno-associated virus (AAV) vector, and cleavage of the target sites flanking the antibody coding sequence removes the inverted terminal repeats of the AAV.

12. The use of any preceding claim, wherein the heavy chain coding sequence comprises V_H, D_H, and J_H segments, and the light chain coding sequence comprises V_L and J_L gene segments.

13. The use of any preceding claim, wherein the exogenous secretion signal sequence is a ROR1 secretion signal sequence.

14. The use of any preceding claim, wherein the disease-associated antigen is a cancer-associated antigen.

15. The use of any one of claims 1-13, wherein the disease-associated antigen is an infectious-disease-associated antigen.

16. The use of claim 15, wherein the disease-associated antigen is a viral antigen.

17. The use of claim 16, wherein the viral antigen is an influenza antigen or a Zika antigen.

18. The use of claim 17, wherein the viral antigen is an influenza hemagglutinin antigen.

19. The use of claim 18, wherein the antibody comprises a light chain comprising three light chain CDRs and a heavy chain comprising three heavy chain CDRs, wherein:

(I) the light chain comprises, consists essentially of, or consists of the sequence set forth in SEQ ID NO: 18 and the heavy chain comprises, consists essentially of, or consists of the sequence set forth in SEQ ID NO: 20,

or wherein the three light chain CDRs comprise, consist essentially of, or consist of the sequences set forth in SEQ ID NOS: 76-78, respectively, and the three heavy chain

CDRs comprise, consist essentially of, or consist of the sequences set forth in SEQ ID NOS: 79-81, respectively; or

(II) the light chain comprises, consists essentially of, or consists of the sequence set forth in SEQ ID NO: 126 and the heavy chain comprises, consists essentially of, or consists of the sequence set forth in SEQ ID NO: 128,

or wherein the three light chain CDRs comprise, consist essentially of, or consist of the sequences set forth in SEQ ID NOS: 129-131, respectively, and the three heavy chain CDRs comprise, consist essentially of, or consist of the sequences set forth in SEQ ID NOS: 132-134, respectively.

20. The use of claim 17, wherein the viral antigen is a Zika Envelope (Env) antigen.

21. The use of claim 20, wherein the antibody comprises a light chain comprising three light chain CDRs and a heavy chain comprising three heavy chain CDRs, wherein:

the light chain comprises, consists essentially of, or consists of the sequence set forth in SEQ ID NO: 3 and the heavy chain comprises, consists essentially of, or consists of the sequence set forth in SEQ ID NO: 5,

or wherein the three light chain CDRs comprise, consist essentially of, or consist of the sequences set forth in SEQ ID NOS: 64-66, respectively, and the three heavy chain CDRs comprise, consist essentially of, or consist of the sequences set forth in SEQ ID NOS: 67-69, respectively.

22. The use of claim 20, wherein the antibody comprises a light chain comprising three light chain CDRs and a heavy chain comprising three heavy chain CDRs, wherein:

the light chain comprises, consists essentially of, or consists of the sequence set forth in SEQ ID NO: 13 and the heavy chain comprises, consists essentially of, or consists of the sequence set forth in SEQ ID NO: 15,

or wherein the three light chain CDRs comprise, consist essentially of, or consist of the sequences set forth in SEQ ID NOS: 70-72, respectively, and the three heavy chain CDRs

comprise, consist essentially of, or consist of the sequences set forth in SEQ ID NOS: 73-75, respectively.

23. The use of claim 15, wherein the disease-associated antigen is a bacterial antigen, optionally wherein the bacterial antigen is a *Pseudomonas aeruginosa* PcrV antigen.

24. The use of any preceding claim, wherein the antibody is a neutralizing antibody.

25. The use of claim 24, wherein the antibody is a broadly neutralizing antibody.

26. The use of any preceding claim, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are in separate delivery vehicles.

27. The use of any one of claims 1-25, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are together in the same delivery vehicle.

28. The use of any preceding claim, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are to be introduced simultaneously.

29. The use of any one of claims 1-26, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are to be introduced sequentially.

30. The use of any preceding claim, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are to be introduced in single doses.

31. The use of any one of claims 1-29, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and/or the exogenous donor nucleic acid are to be introduced in multiple doses.

32. The use of any preceding claim, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are to be delivered via intravenous injection.

33. The use of any preceding claim, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are associated with a lipid nanoparticle or in an adeno-associated virus (AAV) vector, optionally wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are both in AAV vectors, and optionally wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are in two different AAV vectors.

34. The use of claim 33, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent is associated with the lipid nanoparticle.

35. The use of claim 34, wherein the nuclease agent is a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated 9 (Cas9) protein and a guide RNA (gRNA).

36. The use of claim 35, wherein the Cas9 is in the form of mRNA, and the gRNA is in the form of RNA.

37. The use of any one of claims 33-36, wherein the exogenous donor nucleic acid is in the AAV vector.

38. The use of claim 37, wherein the AAV is a single-stranded AAV (ssAAV).

39. The use of claim 37, wherein the AAV is a self-complementary AAV (scAAV).

40. The use of any one of claims 37-39, wherein the AAV is AAV8 or AAV2/8.

41. The use of any one of claims 1-33, wherein the nuclease agent comprises a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated 9 (Cas9) and a guide RNA (gRNA), wherein the gRNA and an mRNA encoding the Cas9 are associated with a lipid nanoparticle, and the exogenous donor nucleic acid is in an AAV8 or AAV2/8 vector.

42. The use of any one of claims 1-33, wherein the nuclease agent comprises a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated 9 (Cas9) and a guide RNA (gRNA), wherein a DNA encoding the Cas9 is in a first AAV8 vector or a first AAV2/8 vector, and the exogenous donor nucleic acid and a DNA encoding the gRNA are in a second AAV8 vector or a second AAV2/8 vector.

43. The use of any preceding claim, wherein expression of the antibody in the animal results in plasma levels of at least about 2.5 µg/mL, at least about 5 µg/mL, at least about 10 µg/mL, at least about 100 µg/mL, at least about 200 µg/mL, at least about 300 µg/mL, at least about 400 µg/mL, at least about 500 µg/mL, at least about 600 µg/mL, at least about 700 µg/mL, at least about 800 µg/mL, at least about 900 µg/mL, or at least about 1000 µg/mL about 2 weeks, about 4 weeks, about 8 weeks, about 12 weeks, or about 16 weeks after introducing the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor sequence.

44. The use of any preceding claim, wherein the animal is a non-human animal.

45. The use of claim 44, wherein the animal is a non-human mammal.

46. The use of claim 45, wherein the non-human mammal is a rat or a mouse.

47. The use of any one of claims 1-43, wherein the animal is a human.

48. The use of any preceding claim, wherein the nuclease agent is a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated 9 (Cas9) protein and a guide RNA (gRNA),

wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor sequence are associated with a lipid nanoparticle, are in AAV8 vectors, or are in AAV2/8 vectors,

wherein the antibody coding sequence is to be inserted into the first intron of the albumin locus via non-homologous end joining in the one or more liver cells in the animal,

wherein the antibody targets a viral antigen or a bacterial antigen, and

wherein the antibody is a broadly neutralizing antibody.

49. The use of claim 48, wherein the exogenous secretion signal sequence is an ROR1 secretion signal sequence.

50. A pharmaceutical composition for use in treating a disease or preventing an infectious disease in a subject, comprising a nuclease agent or one or more nucleic acids encoding the nuclease agent and an exogenous donor nucleic acid comprising an antibody coding sequence,

wherein the nuclease agent is a zinc finger nuclease (ZFN), a Transcription Activator-Like Effector Nuclease (TALEN), or a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated (Cas) protein and a guide RNA (gRNA),

wherein the nuclease agent targets and cleaves a target site in intron 1 of an albumin locus in one or more liver cells of the subject, wherein the exogenous donor nucleic acid is to be inserted into intron 1 of the albumin locus in the one or more liver cells of the subject to produce a modified albumin locus,

wherein the antibody is not a single-chain antibody,

wherein the antibody comprises a heavy chain and a separate light chain,

wherein the heavy chain coding sequence is upstream of the light chain coding sequence in the antibody coding sequence,

wherein the heavy chain and the light chain are linked by a 2A peptide,

wherein the 2A peptide is a T2A peptide,

wherein a nucleic acid encoding a furin cleavage site is included between the heavy chain coding sequence and the light chain coding sequence, and wherein the furin cleavage site is upstream of the 2A peptide,

wherein the heavy chain coding sequence is operably linked to an endogenous albumin secretion signal sequence in the albumin locus, and the antibody coding sequence comprises an exogenous secretion signal sequence upstream of the light chain coding sequence, wherein the inserted antibody coding sequence is operably linked to an endogenous albumin promoter in the albumin locus, and wherein the antibody is expressed in the subject and targets an antigen associated with the disease.

51. The composition for use of claim 50, wherein the nuclease agent is the Cas protein and the gRNA, wherein the Cas protein is a Cas9 protein, and wherein the gRNA comprises:

- (a) a CRISPR RNA (crRNA) that targets the target site, wherein the target site is immediately flanked by a Protospacer Adjacent Motif (PAM) sequence; and
- (b) a trans-activating CRISPR RNA (tracrRNA).

52. The composition for use of claim 51, wherein the gRNA comprises 2'-O-methyl analogs and 3' phosphorothioate internucleotide linkages at the first three 5' and 3' terminal RNA residues.

53. The composition for use of any one of claims 50-52, wherein the antibody coding sequence is to be inserted via non-homologous end joining.

54. The composition for use of any one of claims 50-52, wherein the antibody coding sequence is to be inserted via homology-directed repair.

55. The composition for use of any one of claims 50-53, wherein the exogenous donor nucleic acid does not comprise homology arms.

56. The composition for use of any one of claims 50-55, wherein the exogenous donor nucleic acid is single-stranded.

57. The composition for use of any one of claims 50-55, wherein the exogenous donor nucleic acid is double-stranded.

58. The composition for use of any one of claims 50-57, wherein the antibody coding sequence in the exogenous donor nucleic acid is flanked on each side by the target site for the nuclease agent.

59. The composition for use of claim 58, wherein the target site in the safe harbor locus is no longer present if the antibody coding sequence is inserted into the safe harbor locus in the correct orientation but it is reformed if the antibody coding sequence is inserted into the safe harbor locus in the opposite orientation.

60. The composition for use of claim 58 or 59, wherein the exogenous donor nucleic acid is in an adeno-associated virus (AAV) vector, and cleavage of the target sites flanking the antibody coding sequence removes the inverted terminal repeats of the AAV.

61. The composition for use of any one of claims 50-60, wherein the heavy chain coding sequence comprises V_H , D_H , and J_H segments, and the light chain coding sequence comprises V_L and J_L gene segments.

62. The composition for use of any one of claims 50-61, wherein the exogenous secretion signal sequence is a ROR1 secretion signal sequence.

63. The composition for use of any one of claims 50-62, wherein the disease-associated antigen is a cancer-associated antigen.

64. The composition for use of any one of claims 50-62, wherein the disease-associated antigen is an infectious-disease-associated antigen.

65. The composition for use of claim 64, wherein the disease-associated antigen is a viral antigen.

66. The composition for use of claim 65, wherein the viral antigen is an influenza antigen or a Zika antigen.

67. The composition for use of claim 66, wherein the viral antigen is an influenza hemagglutinin antigen.

68. The composition for use of claim 67, wherein the antibody comprises a light chain comprising three light chain CDRs and a heavy chain comprising three heavy chain CDRs, wherein:

(I) the light chain comprises the sequence set forth in SEQ ID NO: 18 and the heavy chain comprises the sequence set forth in SEQ ID NO: 20,

or wherein the three light chain CDRs comprise the sequences set forth in SEQ ID NOS: 76-78, respectively, and the three heavy chain CDRs comprise the sequences set forth in SEQ ID NOS: 79-81, respectively; or

(II) the light chain the sequence set forth in SEQ ID NO: 126 and the heavy chain comprises the sequence set forth in SEQ ID NO: 128,

or wherein the three light chain CDRs comprise the sequences set forth in SEQ ID NOS: 129-131, respectively, and the three heavy chain CDRs comprise the sequences set forth in SEQ ID NOS: 132-134, respectively.

69. The composition for use of claim 66, wherein the viral antigen is a Zika Envelope (Env) antigen.

70. The composition for use of claim 69, wherein the antibody comprises a light chain comprising three light chain CDRs and a heavy chain comprising three heavy chain CDRs, wherein:

the light chain comprises the sequence set forth in SEQ ID NO: 3 and the heavy chain comprises the sequence set forth in SEQ ID NO: 5,

or wherein the three light chain CDRs comprise the sequences set forth in SEQ ID NOS: 64-66, respectively, and the three heavy chain CDRs comprise the sequences set forth in SEQ ID NOS: 67-69, respectively.

71. The composition for use of claim 69, wherein the antibody comprises a light chain comprising three light chain CDRs and a heavy chain comprising three heavy chain CDRs, wherein:

the light chain comprises the sequence set forth in SEQ ID NO: 13 and the heavy chain comprises the sequence set forth in SEQ ID NO: 15,

or wherein the three light chain CDRs comprise the sequences set forth in SEQ ID NOS: 70-72, respectively, and the three heavy chain CDRs comprise the sequences set forth in SEQ ID NOS: 73-75, respectively.

72. The composition for use of claim 64, wherein the disease-associated antigen is a bacterial antigen, optionally wherein the bacterial antigen is a *Pseudomonas aeruginosa* PcrV antigen.

73. The composition for use of any one of claims 50-72, wherein the antibody is a neutralizing antibody.

74. The composition for use of claim 73, wherein the antibody is a broadly neutralizing antibody.

75. The composition for use of any one of claims 50-74, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are in separate delivery vehicles.

76. The composition for use of any one of claims 50-74, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are together in the same delivery vehicle.

77. The composition for use of any one of claims 50-76, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are to be introduced simultaneously.

78. The composition for use of any one of claims 50-75, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are to be introduced sequentially.

79. The composition for use of any one of claims 50-78, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are to be introduced in single doses.

80. The composition for use of any one of claims 50-78, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and/or the exogenous donor nucleic acid are to be introduced in multiple doses.

81. The composition for use of any one of claims 50-80, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are to be delivered via intravenous injection.

82. The composition for use of any one of claims 50-81, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are associated with a lipid nanoparticle or are in an adeno-associated virus (AAV) vector, optionally wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are both in AAV vectors, and optionally wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor nucleic acid are in two different AAV vectors.

83. The composition for use of claim 82, wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent is associated with the lipid nanoparticle.

84. The composition for use of claim 83, wherein the nuclease agent is a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated 9 (Cas9) protein and a guide RNA (gRNA).

85. The composition for use of claim 84, wherein the Cas9 is in the form of mRNA, and the gRNA is in the form of RNA.

86. The composition for use of any one of claims 82-85, wherein the exogenous donor nucleic acid is in the AAV vector.

87. The composition for use of claim 86, wherein the AAV is a single-stranded AAV (ssAAV).

88. The composition for use of claim 86, wherein the AAV is a self-complementary AAV (scAAV).

89. The composition for use of any one of claims 86-88, wherein the AAV is AAV8 or AAV2/8.

90. The composition for use of any one of claims 50-82, wherein the nuclease agent comprises a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated 9 (Cas9) and a guide RNA (gRNA), wherein the gRNA and an mRNA encoding the Cas9 are associated with a lipid nanoparticle, and the exogenous donor nucleic acid is in an AAV8 vector or an AAV2/8 vector.

91. The composition for use of any one of claims 50-82, wherein the nuclease agent comprises a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated 9 (Cas9) and a guide RNA (gRNA), wherein a DNA encoding the Cas9 is in a first AAV8 vector or a first AAV2/8 vector, and the exogenous donor nucleic acid and a DNA encoding the gRNA are in a second AAV8 vector or a second AAV2/8 vector.

92. The composition for use of any one of claims 50-91, wherein expression of the antibody in the subject results in plasma levels of at least about 2.5 µg/mL, at least about 5 µg/mL, at least about 10 µg/mL, at least about 100 µg/mL, at least about 200 µg/mL, at least about 300 µg/mL, at least about 400 µg/mL, at least about 500 µg/mL, at least about 600 µg/mL, at least about 700 µg/mL, at least about 800 µg/mL, at least about 900 µg/mL, or at least about 1000 µg/mL about 2 weeks, about 4 weeks, about 8 weeks, about 12 weeks, or about 16 weeks after introducing the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor sequence.

93. The composition for use of any one of claims 50-92, wherein the subject is a non-human animal.

94. The composition for use of claim 93, wherein the subject is a non-human mammal.

95. The composition for use of claim 94, wherein the non-human mammal is a rat or a mouse.

96. The composition for use of any one of claims 50-92, wherein the subject is a human.

97. The composition for use of any one of claims 50-96, wherein the nuclease agent is a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated 9 (Cas9) protein and a guide RNA (gRNA),

wherein the nuclease agent or the one or more nucleic acids encoding the nuclease agent and the exogenous donor sequence are associated with a lipid nanoparticle, are in AAV8 vectors, or are in AAV2/8 vectors,

wherein the antibody coding sequence is to be inserted into the first intron of the albumin locus via non-homologous end joining in the one or more liver cells in the subject,

wherein the antibody targets a viral antigen or a bacterial antigen, and

wherein the antibody is a broadly neutralizing antibody.

98. The composition for use of claim 97, wherein the exogenous secretion signal sequence is an ROR1 secretion signal sequence.