CLAIMS

1. Use of a population of pluripotent cells comprising a transgene that encodes a C1-esterase inhibitor (C1-INH) protein in the manufacture of a medicament for treating hereditary angioedema (HAE) in a patient in need thereof.

2. Use of a population of pluripotent cells comprising a transgene that encodes a C1-INH protein in the manufacture of a medicament for inducing sustained remission of HAE in a patient in need thereof.

3. Use of a population of pluripotent cells comprising a transgene that encodes a C1-INH protein in the manufacture of a medicament for preventing angioedema attacks in a patient diagnosed as having HAE.

4. Use of a population of pluripotent cells comprising a transgene that encodes a C1-INH protein in the manufacture of a medicament for reducing the risk of recurrent angioedema attacks in a patient diagnosed as having HAE.

5. The use of claim 3 or 4, wherein the angioedema attacks occur in the patient's skin, mucosa, gastrointestinal tract, and/or genitourinary region.

6. Use of a population of pluripotent cells comprising a transgene that encodes a C1-INH protein in the manufacture of a medicament for reducing the risk of developing laryngeal angioedema attacks in a patient diagnosed as having HAE.

7. The use of any one of claims 1-6, wherein the pluripotent cells are hematopoietic stem cells (HSCs), hematopoietic progenitor cells (HPCs), embryonic stem cells, induced pluripotent stem cells, or CD34+ cells.

8. The use of claim 7, wherein the CD34+ cells are myeloid progenitor cells.

9. The use of any one of claims 1-8, wherein:

(i) the population of pluripotent cells is to be administered systemically to the patient;

(ii) the pluripotent cells are autologous with respect to the patient or allogeneic with respect to the patient; and/or

(iii) the cells are transduced ex vivo to express C1-INH, the pluripotent cells are transfected ex vivo to express C1-INH, or the pluripotent cells are obtained by delivering to the cells a nuclease that catalyzes a

single-strand break or a double-strand break at a target position within the genome of the cell, optionally wherein the target position is near or within a gene encoding an endogenous C1-INH protein.

10. The use of claim 9, wherein:

(i) the population of pluripotent cells is to be administered to the patient by way of intravenous injection;

(ii) the pluripotent cells are HLA-matched to the patient;

(iii) the cells are transduced with a viral vector selected from the group consisting of a Retroviridae family virus, an adenovirus, a parvovirus, a coronavirus, a rhabdovirus, a paramyxovirus, a picornavirus, an alphavirus, a herpes virus, and a poxvirus;

(iv) the pluripotent cells are transfected using a cationic polymer, diethylaminoethyldextran, polyethylenimine, a cationic lipid, a liposome, calcium phosphate, an activated dendrimer, and/or a magnetic bead;

(v) the pluripotent cells are transfected by way of electroporation, Nucleofection, squeeze-poration, sonoporation, optical transfection, Magnetofection, and/or impalefection;

(vi) the nuclease is delivered to the cells in combination with a guide RNA (gRNA) that hybridizes to the target position within the genome of the cell;

(vii) the nuclease is a clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein;

(viii) the nuclease is a transcription activator-like effector nuclease, a meganuclease, or a zinc finger nuclease; and/or

(ix) the cells are additionally contacted with a template nucleic acid encoding C1-INH while the cells are contacted with the nuclease.

11. The use of claim 10, wherein:

(i) the viral vector is a Retroviridae family viral vector;

(ii) the Retroviridae family viral vector comprises a central polypurine tract, a woodchuck hepatitis virus post-transcriptional regulatory element, a 5'-LTR, HIV signal sequence, HIV Psi signal 5'-splice site, delta-GAG element, 3'-splice site, and a 3'-self inactivating LTR;

(iii) the viral vector is a pseudotyped viral vector;

(iv) the CRISPR-associated protein is CRISPR-associated protein 9 (Cas9) or CRISPR-associated protein 12a (Cas12a);

(v) the template nucleic acid molecule encoding C1-INH comprises a 5’ homology arm and a 3’ homology arm having nucleic acid sequences that are sufficiently similar to the nucleic acid sequences located 5’ to the target position and 3’ to the target position, respectively, to promote homologous recombination; and/or

(vi) the nuclease, gRNA, and/or template nucleic acid are delivered to the cells by contacting the cells with a viral vector that encodes the nuclease, gRNA, and/or template nucleic acid.

12. The use of claim 11, wherein:

(i) the Retroviridae family viral vector is a lentiviral vector, an alpharetroviral vector, or a gammaretroviral vector;

(ii) the pseudotyped viral vector is selected from the group consisting of a pseudotyped adenovirus, a pseudotyped parvovirus, a pseudotyped coronavirus, a pseudotyped rhabdovirus, a pseudotyped paramyxovirus, a pseudotyped picornavirus, a pseudotyped alphavirus, a pseudotyped herpes virus, a pseudotyped poxvirus, and a pseudotyped Retroviridae family virus; and/or

(iii) the pseudotyped viral vector comprises one or more envelope proteins from a virus selected from vesicular stomatitis virus (VSV), RD114 virus, murine leukemia virus (MLV), feline leukemia virus (FeLV), Venezuelan equine encephalitis virus (VEE), human foamy virus (HFV), walleye dermal sarcoma virus (WDSV), Semliki Forest virus (SFV), Rabies virus, avian leukosis virus (ALV), bovine immunodeficiency virus (BIV), bovine leukemia virus (BLV), Epstein-Barr virus (EBV), Caprine arthritis encephalitis virus (CAEV), Sin Nombre virus (SNV), Cherry Twisted Leaf virus (ChTLV), Simian T-cell leukemia virus (STLV), Mason-Pfizer monkey virus (MPMV), squirrel monkey retrovirus (SMRV), Rous-associated virus (RAV), Fujinami sarcoma virus (FuSV), avian carcinoma virus (MH2), avian encephalomyelitis virus (AEV), Alfa mosaic virus (AMV), avian sarcoma virus CT10, and equine infectious anemia virus (EIAV).

13. The use of claim 12, wherein:

(i) the pseudotyped viral vector is a lentiviral vector; and/or

(ii) the pseudotyped viral vector comprises a VSV-G envelope protein.

14. The use of claim 11, wherein:

(i) the viral vector that encodes the nuclease, gRNA, and/or template nucleic acid is an AAV, an adenovirus, a parvovirus, a coronavirus, a rhabdovirus, a paramyxovirus, a picornavirus, an alphavirus, a herpes virus, a poxvirus, or a Retroviridae family virus;

(ii) the viral vector that encodes the nuclease, gRNA, and/or template nucleic acid is an integration-deficient lentiviral vector; or

(iii) the viral vector that encodes the nuclease, gRNA, and/or template nucleic acid is an AAV selected from the group consisting of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, and AAVrh74.

15. The use of claim 14, wherein the viral vector that encodes the nuclease, gRNA, and/or template nucleic acid is a Retroviridae family virus.

16. The use of claim 15, wherein:

(i) the Retroviridae family virus is a lentiviral vector, alpharetroviral vector, or gammaretroviral vector; and/or

(ii) the Retroviridae family virus that encodes the nuclease, gRNA, and/or template nucleic acid comprises a central polypurine tract, a woodchuck hepatitis virus post-transcriptional regulatory element, a 5'-LTR, HIV signal sequence, HIV Psi signal 5'-splice site, delta-GAG element, 3'-splice site, and a 3'-self inactivating LTR.

17. The use of any one of claims 1-16, wherein prior to administering the population of pluripotent cells to the patient, a population of precursor cells is to be isolated from the patient or a donor, and wherein the precursor cells are expanded ex vivo to yield the population of cells being administered to the patient.

18. The use of claim 17, wherein:

(i) the precursor cells are CD34+ HSCs, and wherein the precursor cells are expanded without substantial loss of HSC functional potential; and/or

(ii) prior to isolation of the precursor cells from the patient or donor, the patient or donor is to be administered one or more pluripotent cell mobilization agents.

19. The use of any one of claims 1-18, wherein:

(i) prior to administering the population of pluripotent cells to the patient, a population of endogenous pluripotent cells is ablated in the patient by administration of one or more conditioning agents to the patient; or

(ii) the treating comprises ablating a population of endogenous pluripotent cells in the patient by administering to the patient one or more conditioning agents prior to administering the population of pluripotent cells to the patient.

20. The use of claim 19, wherein:

(i) the one or more conditioning agents are non-myeloablative conditioning agents;

(ii) the one or more conditioning agents deplete a population of CD34+ cells in the patient; and/or

(iii) the one or more conditioning agents comprise an antibody or antigen-binding fragment thereof.

21. The use of claim 20, wherein:

(i) the depleted CD34+ cells are myeloid progenitor cells;

(ii) the antibody or antigen-binding fragment thereof binds to CD117, HLA-DR, CD34, CD90, CD45, or CD133; and/or

(iii) the antibody or antigen-binding fragment thereof is conjugated to a cytotoxin.

22. The use of claim 21, wherein the antibody or antigen-binding fragment thereof binds to CD117.

23. The use of any one of claims 1-22, wherein upon administration of the population of pluripotent cells to the patient, the administered cells, or progeny thereof, differentiate into one or more cell types selected from megakaryocytes, thrombocytes, platelets, erythrocytes, mast cells, myeoblasts, basophils, neutrophils, eosinophils, microglia, granulocytes, monocytes, osteoclasts, antigen-presenting cells, macrophages, dendritic cells, natural killer cells, T-lymphocytes, and B-lymphocytes.

24. The use of any one of claims 1-23, wherein:

(i) the transgene is operably linked to a ubiquitous promoter;

(ii) the transgene is operably linked to a tissue-specific promoter;

(iii) the transgene is operably linked to a myeloid cell-specific promoter; or

(iv) the transgene is operably linked to a CD11b promoter, sp146/p47 promoter, CD68 promoter, sp146/gp9 promoter, elongation factor 1 α (EF1α) promoter, EF1α short form (EFS) promoter, phosphoglycerate kinase (PGK) promoter, α-globin promoter, β-globin promoter, DC172 promoter, human serum albumin promoter, alpha1 antitrypsin promoter, thyroxine binding globulin promoter, or C1-INH promoter.

25. The use of any one of claims 1-24, wherein:

(i) the transgene is operably linked to an enhancer;

(ii) the transgene is operably linked to a miRNA targeting sequence;

(iii) the patient is a mammal, and the cells are mammalian cells;

(iv) the patient has a loss-of-function mutation in an endogenous gene encoding C1-INH;

(v) the patient has a mutation in an endogenous gene encoding C1-INH that causes (a) a deletion or (b) expression of a truncated transcript;

(vi) the patient has a mutation in a gene encoding coagulation factor XII (F12);

(vii) the patient has previously been treated with one or more immunosuppressive agents, biologic agents, and/or corticosteroids;

(viii) the patient has previously been treated with one or more therapeutic agents selected from the group consisting of C1-esterase inhibitor, icatibant, and ecallantide;

(ix) the patient has previously been treated with one or more prophylactic agents selected from the group consisting of Cinryze, Haegarda, Takhzyro, and an androgen;

(x) the patient is less than 12 years old, or the patient is more than 6 years old;

(xi) prior to administering the population of pluripotent cells to the patient, the patient exhibits angioedema attacks with a frequency of from one to ten times per month or prior to administering the

population of pluripotent cells to the patient, the patient exhibits angioedema attacks with a frequency of one or two times per week;

(xii) after administering the population of pluripotent cells to the patient, the patient exhibits sustained disease remission;

(xiii) after administering the population of pluripotent cells to the patient, the patient does not exhibit an angioedema attack for a period of from about two months to about one year;

(xiv) after administering the population of pluripotent cells to the patient, the patient exhibits a serum concentration of C1-INH protein of at least about 7 mg/dl;

(xv) after administering the population of pluripotent cells to the patient, the patient exhibits a serum concentration of C1-INH protein that is from about 40% to about 60% of a serum concentration of C1-INH protein exhibited by a subject that does not have HAE, optionally wherein the subject (a) is the same gender as the patient and/or (b) has the same body mass index as the patient; and/or

(xvi) administration of the population of pluripotent cells to the patient reduces the patient's risk of suffocation due to laryngeal angioedema attacks.

26. The use of claim 25, wherein:

(i) the enhancer comprises a β-globin locus control region (βLCR);

(ii) the miRNA targeting sequence has complementarity to a miRNA that is endogenously expressed in a tissue in which expression of C1-INH is undesirable;

(iii) the mammal is a human and the cells are human cells;

(iv) the patient has not responded to treatment with the one or more immunosuppressive agents, biologic agents, and/or corticosteroids;

(v) the patient has not responded to treatment with the one or more therapeutic agents;

(vi) the patient has not responded to treatment with the one or more prophylactic agents;

(vii) the patient is less than 6 years old, or the patient is more than 12 years old; and/or

(viii) after administering the population of pluripotent cells to the patient, the patient exhibits a serum concentration of C1-INH protein of from about 15 mg/dl to about 35 mg/dl.

27. The use of claim 25, wherein:

(i) the mutation is a deletion or substitution of an amino acid located within the reactive center loop (RCL) of C1-INH;

(ii) the mutation is a deletion or substitution of K251; or

(iii) the mutation is selected from the group consisting of A436T, R444H, R444C, R444S, V432E, A443V, Y199TER, I462S, and R378C.

28. The use of claim 25 or 27, wherein the mutation is heterozygous or homozygous.

29. Use of a lentiviral vector comprising a transgene that encodes a C1-INH protein in the manufacture of a medicament for treating HAE in a patient in need thereof.

30. Use of a lentiviral vector comprising a transgene that encodes a C1-INH protein in the manufacture of a medicament for inducing sustained remission of HAE in a patient in need thereof.

31. Use of a lentiviral vector comprising a transgene that encodes a C1-INH protein in the manufacture of a medicament for preventing angioedema attacks in a patient diagnosed as having HAE.

32. Use of a lentiviral vector comprising a transgene that encodes a C1-INH protein in the manufacture of a medicament for reducing the risk of recurrent angioedema attacks in a patient diagnosed as having HAE.

33. The use of claim 31 or 32, wherein the angioedema attacks occur in the patient's skin, mucosa, gastrointestinal tract, and/or genitourinary region.

34. Use of a lentiviral vector comprising a transgene that encodes a C1-INH protein in the manufacture of a medicament for reducing the risk of developing laryngeal angioedema attacks in a patient diagnosed as having HAE.

35. The use of any one of claims 29-34, wherein:

(i) the lentiviral vector is to be administered systemically to the patient;

(ii) the lentiviral vector comprises a central polypurine tract, a woodchuck hepatitis virus post-transcriptional regulatory element, a 5'-LTR, HIV signal sequence, HIV Psi signal 5'-splice site, delta-GAG element, 3'-splice site, and a 3'-self inactivating LTR;

(iii) the lentiviral vector is pseudotyped;

(iv) the transgene is operably linked to a ubiquitous promoter, a tissue-specific promoter, a hepatocyte-specific promoter, a transthyretin promoter, CD11b promoter, sp146/p47 promoter, CD68 promoter, sp146/gp9 promoter, EF1α promoter, EFS promoter, PGK promoter, α-globin promoter, β-globin promoter, DC172 promoter, human serum albumin promoter, alpha1 antitrypsin promoter, thyroxine binding globulin promoter, or C1-INH promoter;

(v) the transgene is operably linked to an enhancer;

(vi) the transgene is operably linked to a miRNA targeting sequence;

(vii) the patient is a mammal;

(viii) the patient has a loss-of-function mutation in an endogenous gene encoding C1-INH;

(ix) the patient has a mutation in an endogenous gene encoding C1-INH that causes (a) a deletion or (b) expression of a truncated transcript;

(x) the patient has a mutation in a gene encoding F12;

(xi) the patient has previously been treated with one or more immunosuppressive agents, biologic agents, and/or corticosteroids;

(xii) the patient has previously been treated with one or more therapeutic agents selected from the group consisting of Berinert, Ruconest, Firazyr, and Kalbitor;

(xiii) the patient has previously been treated with one or more prophylactic agents selected from the group consisting of Cinryze, Haegarda, Takhzyro, and an androgen;

(xiv) the patient is less than 12 years old, or the patient is more than 6 years old;

(xv) prior to administering the lentiviral vector to the patient, the patient exhibits angioedema attacks with a frequency of from one to ten times per month or prior to administering the lentiviral vector to the patient, the patient exhibits angioedema attacks with a frequency of one or two times per week;

(xvi) after administering the lentiviral vector to the patient, the patient exhibits sustained disease remission;

(xvii) after administering the lentiviral vector to the patient, the patient does not exhibit an angioedema attack for a period of from about two months to about one year;

(xviii) after administering the lentiviral vector to the patient, the patient exhibits a serum concentration of C1-INH protein of at least about 7 mg/dl;

(xix) after administering the lentiviral vector to the patient, the patient exhibits a serum concentration of C1-INH protein that is from about 40% to about 60% of a serum concentration of C1-INH protein exhibited by a subject that does not have HAE, optionally wherein the subject (a) is the same gender as the patient and/or (b) has the same body mass index as the patient; and/or

(xx) administration of the lentiviral vector to the patient reduces the patient's risk of suffocation due to laryngeal angioedema attacks.

36. The use of claim 35, wherein:

(i) the lentiviral vector is to be administered to the patient by way of intravenous injection;

(ii) the lentiviral vector comprises one or more envelope proteins from a virus selected from VSV, RD114 virus, MLV, FeLV, VEE, HFV, WDSV, SFV, Rabies virus, ALV, BIV, BLV, EBV, CAEV, SNV, ChTLV, STLV, MPMV, SMRV, RAV, FuSV, MH2, AEV, AMV, avian sarcoma virus CT10, and EIAV;

(iii) the enhancer comprises a βLCR;

(iv) the miRNA targeting sequence has complementarity to a miRNA that is endogenously expressed in a tissue in which expression of C1-INH is undesirable;

(v) the mammal is a human;

(vi) the patient has not responded to treatment with the one or more immunosuppressive agents, biologic agents, and/or corticosteroids;

(vii) the patient has not responded to treatment with the one or more therapeutic agents;

(viii) the patient has not responded to treatment with the one or more prophylactic agents;

(ix) the patient is less than 6 years old, or the patient is more than 12 years old; and/or

(x) after administering the lentiviral vector to the patient, the patient exhibits a serum concentration of C1-INH protein of from about 15 mg/dl to about 35 mg/dl.

37. The use of claim 36, wherein the lentiviral vector comprises a VSV-G envelope protein.

38. The use of claim 35, wherein:

(i) the mutation is a deletion or substitution of an amino acid located within the RCL of C1-INH;

(ii) the mutation is a deletion or substitution of K251; or

(iii) the mutation is selected from the group consisting of A436T, R444H, R444C, R444S, V432E, A443V, Y199TER, I462S, and R378C.

39. The use of claim 35 or 38, wherein the mutation is heterozygous or homozygous.

40. A pharmaceutical composition comprising (i) a population of pluripotent cells comprising a transgene that encodes a C1-INH protein and (ii) one or more carriers, diluents, and/or excipients.

41. The pharmaceutical composition of claim 40, wherein the cells are human cells.

42. The pharmaceutical composition of claim 40 or 41, wherein:

(i) the cells are HSCs or HPCs;

(ii) the cells are embryonic stem cells;

(iii) the cells are induced pluripotent stem cells; or

(iv) the cells are CD34+ cells.

43. The pharmaceutical composition of claim 42, wherein the CD34+ cells are myeloid progenitor cells.

44. The pharmaceutical composition of any one of claims 40-43, wherein the composition is formulated for administration to a human patient.

45. The pharmaceutical composition of claim 44, wherein the composition is formulated for intravenous injection to the human patient.

46. The pharmaceutical composition of claim 44 or 45, wherein the cells are autologous with respect to the patient, or the cells are allogeneic with respect to the patient.

47. The pharmaceutical composition of claim 46, wherein the cells are HLA-matched to the patient.

48. The pharmaceutical composition of any one of claims 40-47, wherein:

(i) the transgene is operably linked to a ubiquitous promoter;

(ii) the transgene is operably linked to a tissue-specific promoter;

(iii) the transgene is operably linked to a myeloid cell-specific promoter; or

(iv) the transgene is operably linked to a CD11b promoter, sp146/p47 promoter, CD68 promoter, sp146/gp9 promoter, EF1α promoter, EFS promoter, PGK promoter, α-globin promoter, β-globin promoter, DC172 promoter, human serum albumin promoter, alpha1 antitrypsin promoter, thyroxine binding globulin promoter, or C1-INH promoter.

49. The pharmaceutical composition of any one of claims 40-48, wherein the transgene is operably linked to an enhancer.

50. The pharmaceutical composition of claim 49, wherein the enhancer comprises a βLCR.

51. The pharmaceutical composition of any one of claims 40-50, wherein the transgene is operably linked to a miRNA targeting sequence.

52. The pharmaceutical composition of claim 51, wherein the miRNA targeting sequence has complementarity to a miRNA that is endogenously expressed in a tissue in which expression of C1-INH is undesirable.

53. A pharmaceutical composition comprising (i) a lentiviral vector comprising a transgene that encodes a C1-INH protein and (ii) one or more carriers, diluents, and/or excipients.

54. The pharmaceutical composition of claim 53, wherein:

(i) the lentiviral vector comprises a central polypurine tract, a woodchuck hepatitis virus post-transcriptional regulatory element, a 5'-LTR, HIV signal sequence, HIV Psi signal 5'-splice site, delta-GAG element, 3'-splice site, and a 3'-self inactivating LTR; and/or

(ii) the lentiviral vector is pseudotyped.

55. The pharmaceutical composition of claim 54, wherein the lentiviral vector comprises one or more envelope proteins from a virus selected from VSV, RD114 virus, MLV, FeLV, VEE, HFV, WDSV, SFV, Rabies virus, ALV, BIV, BLV, EBV, CAEV, SNV, ChTLV, STLV, MPMV, SMRV, RAV, FuSV, MH2, AEV, AMV, avian sarcoma virus CT10, and EIAV.

56. The pharmaceutical composition of claim 55, wherein the lentiviral vector comprises a VSV-G envelope protein.

57. The pharmaceutical composition of any one of claims 53-56, wherein the composition is formulated for administration to a human patient.

58. The pharmaceutical composition of claim 57, wherein the composition is formulated for intravenous injection to the human patient.

59. The pharmaceutical composition of any one of claims 53-58, wherein:

(i) the transgene is operably linked to a ubiquitous promoter;

(ii) the transgene is operably linked to a tissue-specific promoter;

(iii) the transgene is operably linked to a hepatocyte-specific promoter; or

(iv) the transgene is operably linked to a transthyretin promoter, CD11b promoter, sp146/p47 promoter, CD68 promoter, sp146/gp9 promoter, EF1α promoter, EFS promoter, PGK promoter, α-globin promoter, β-globin promoter, DC172 promoter, human serum albumin promoter, alpha1 antitrypsin promoter, thyroxine binding globulin promoter, or C1-INH promoter.

60. The pharmaceutical composition of any one of claims 53-59, wherein the transgene is operably linked to an enhancer.

61. The pharmaceutical composition of claim 60, wherein the enhancer comprises a βLCR.

62. The pharmaceutical composition of any one of claims 53-61, wherein the transgene is operably linked to a miRNA targeting sequence.

63. The pharmaceutical composition of claim 62, wherein the miRNA targeting sequence has complementarity to a miRNA that is endogenously expressed in a tissue in which expression of C1-INH is undesirable.

64. A kit comprising the pharmaceutical composition of any one of claims 40-63, wherein the kit further comprises a package insert instructing a user of the kit to administer the pharmaceutical composition to a human patient having HAE.

65. The kit of claim 64, wherein the package insert instructs a user of the kit to perform the method of any one of claims 1-39.