

COMPOSITIONS AND METHODS FOR TREATING OR PREVENTING HEREDITARY ANGIOEDEMA

Sequence Listing

5 The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. The ASCII copy, created on August 11, 2021, is named 51139-026WO2_Sequence_Listing_8_11_21_ST25.txt and is 6,646 bytes in size.

Field of the Invention

10 The disclosure relates to methods for treating hereditary angioedema by way of modulating gene expression, as well as compositions that may be used in such methods.

Background

15 Hereditary angioedema (HAE) is a disorder that results in recurrent attacks of severe swelling in various body parts, such as the arms, legs, face, intestinal tract, and airway. There is currently no cure for HAE, and long-term, effective treatment options are limited. For patients afflicted with HAE, the disease can have a devastating impact on their lifestyle, as recurrent attacks can happen one or more times per week, with attacks lasting up to three or four days. There remains a need for therapeutic modalities that target underlying causes of HAE to achieve effective amelioration of symptoms and disease remission.

Summary of the Invention

25 The present disclosure relates to compositions and methods for the treatment of hereditary angioedema (HAE). The present disclosure provides compositions and methods for treating or prevent HAE by administering a viral vector or pluripotent cells modified to secrete therapeutic levels of C1-esterase inhibitor (C1-INH) protein.

30 In one ~~aspect~~example, the ~~invention~~disclosure features a method of treating HAE in a patient in need thereof by administering to the patient a population of pluripotent cells including a transgene that encodes a C1-INH protein. In one aspect, the present disclosure refers to 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.

35 In another ~~aspect~~example, the ~~invention~~disclosure features a method of inducing sustained remission of HAE in a patient in need thereof by administering to the patient a population of pluripotent cells including a transgene that encodes a C1-INH protein. In one aspect, the present disclosure refers to 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.

40 In another ~~aspect~~example, the ~~invention~~disclosure features a method of preventing angioedema attacks in a patient diagnosed as having HAE by administering to the patient a population of pluripotent cells including a transgene that encodes a C1-INH protein. In one aspect, the present disclosure refers to 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.

45 In another ~~aspect~~example, the ~~invention~~disclosure features a method of reducing the risk of recurrent angioedema attacks in a patient diagnosed as having HAE by administering to the patient a population of pluripotent cells including a transgene that encodes a C1-INH protein. In one aspect, the present disclosure refers to 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. In some ~~embodiment~~examples, the angioedema attacks occur in the patient's skin, mucosa, gastrointestinal tract, and/or genitourinary region.

In another aspectexample, the inventiondisclosure features a method of reducing the risk of developing laryngeal angioedema attacks in a patient diagnosed as having HAE by administering to the patient a population of pluripotent cells including a transgene that encodes a C1-INH protein. In one aspect, the present disclosure refers to 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.

In some embodimentexamples of any of the above aspects, the C1-INH transgene is a codon optimized transgene.

In some embodimentexamples of any of the above aspects, the pluripotent cells are hematopoietic stem cells (HSCs) or hematopoietic progenitor cells (HPCs).

In some embodimentexamples, the pluripotent cells are embryonic stem cells.

In some embodimentexamples, the pluripotent cells are induced pluripotent stem cells.

In some embodimentexamples, the pluripotent cells are CD34+ cells (e.g., myeloid progenitor cells)

In some embodimentexamples, the population of pluripotent cells is administered systemically (e.g., via intravenous injection) to the patient.

In some embodimentexamples, the pluripotent cells are autologous with respect to the patient.

In some embodimentexamples, the pluripotent cells are allogeneic with respect to the patient.

In some embodimentexamples, the pluripotent cells are HLA-matched to the patient.

In some embodimentexamples, the cells are transduced ex vivo to express C1-INH.

In some embodimentexamples, 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.

In some embodimentexamples, the viral vector is a Retroviridae family viral vector.

In some embodimentexamples, the Retroviridae family viral vector is a lentiviral vector.

In some embodimentexamples, the Retroviridae family viral vector is an alpharetroviral vector or a gammaretroviral vector.

In some embodimentexamples, the Retroviridae family viral vector includes 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.

In some embodimentexamples, the viral vector is a pseudotyped viral vector.

In some embodimentexamples, the pseudotyped viral vector 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.

In some embodimentexamples, the pseudotyped viral vector is a lentiviral vector.

In some embodimentexamples, the pseudotyped viral vector includes 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).

In some [embedimentexamples](#), the pseudotyped viral vector includes a VSV-G envelope protein.

In some [embedimentexamples](#), the pluripotent cells are transfected ex vivo to express C1-INH.

In some [embedimentexamples](#), the pluripotent cells are transfected using a cationic polymer, diethylaminoethyl-dextran, polyethylenimine, a cationic lipid, a liposome, calcium phosphate, an activated dendrimer, and/or a magnetic bead.

In some [embedimentexamples](#), the pluripotent cells are transfected by way of electroporation, Nucleofection, squeeze-poration, sonoporation, optical transfection, Magnetofection, and/or impalefection.

In some [embedimentexamples](#), 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.

In some [embedimentexamples](#), 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.

In some [embedimentexamples](#), the nuclease is a clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein.

In some [embedimentexamples](#), the CRISPR-associated protein is CRISPR-associated protein 9 (Cas9) or CRISPR-associated protein 12a (Cas12a).

In some [embedimentexamples](#), the nuclease is a transcription activator-like effector nuclease, a meganuclease, or a zinc finger nuclease.

In some [embedimentexamples](#), the cells are additionally contacted with a template nucleic acid encoding C1-INH while the cells are contacted with the nuclease.

In some [embedimentexamples](#), the template nucleic acid molecule encoding C1-INH includes 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.

In some [embedimentexamples](#), 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.

In some [embedimentexamples](#), 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.

In some [embedimentexamples](#), the viral vector that encodes the nuclease, gRNA, and/or template nucleic acid is a Retroviridae family virus.

In some [embedimentexamples](#), the Retroviridae family virus is a lentiviral vector, alpharetroviral vector, or gammaretroviral vector.

In some [embedimentexamples](#), the Retroviridae family virus that encodes the nuclease, gRNA, and/or template nucleic acid includes 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.

In some [embedimentexamples](#), the viral vector that encodes the nuclease, gRNA, and/or template nucleic acid is an integration-deficient lentiviral vector.

5 In some [embedimentexamples](#), 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.

In some [embedimentexamples](#), prior to administering the population of pluripotent cells to the patient, a population of precursor cells is isolated from the patient or a donor, and wherein the
10 precursor cells are expanded ex vivo to yield the population of cells being administered to the patient.

In some [embedimentexamples](#), the precursor cells are CD34+ HSCs, and wherein the precursor cells are expanded without substantial loss of HSC functional potential.

In some [embedimentexamples](#), prior to isolation of the precursor cells from the patient or donor, the patient or donor is administered one or more pluripotent cell mobilization agents.

15 In some [embedimentexamples](#), 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.

In some [embedimentexamples](#), method includes ablating a population of endogenous pluripotent cells in the patient by administering to the patient one or more conditioning agents prior to
20 administering the population of pluripotent cells to the patient.

In some [embedimentexamples](#), the one or more conditioning agents are non-myeloablative conditioning agents.

In some [embedimentexamples](#), the one or more conditioning agents deplete a population of CD34+ cells in the patient.

25 In some [embedimentexamples](#), the depleted CD34+ cells are myeloid progenitor cells.

In some [embedimentexample](#)s, the one or more conditioning agents include an antibody or antigen-binding fragment thereof.

In some [embedimentexamples](#), the antibody or antigen-binding fragment thereof binds to CD117, HLA-DR, CD34, CD90, CD45, or CD133.

30 In some [embedimentexamples](#), the antibody or antigen-binding fragment thereof binds to CD117.

In some [embedimentexamples](#), the antibody or antigen-binding fragment thereof is conjugated to a cytotoxin.

In some [embedimentexamples](#), upon administration of the population of pluripotent cells to
35 the patient, the administered cells, or progeny thereof, differentiate into one or more cell types selected from megakaryocytes, thrombocytes, platelets, erythrocytes, mast cells, myeloblasts, basophils, neutrophils, eosinophils, microglia, granulocytes, monocytes, osteoclasts, antigen-presenting cells, macrophages, dendritic cells, natural killer cells, T-lymphocytes, and B-lymphocytes.

In some [embedimentexamples](#), the transgene is operably linked to a ubiquitous promoter. In some
40 some [embedimentexample](#)s, the transgene is operably linked to a tissue-specific promoter. In some [embedimentexamples](#), the transgene is operably linked to a myeloid cell-specific promoter.

In some embodimentexamples, the transgene is operably linked to a CD11b promoter, sp146/p47 promoter, CD68 promoter, sp146/gp9 promoter, elongation factor 1 α (EF1 α) promoter, EF1 α 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.

In some embodimentexamples, the transgene is operably linked to an enhancer.

In some embodimentexamples, the enhancer includes a β -globin locus control region (β LCR).

In some embodimentexamples, the transgene is operably linked to a miRNA targeting sequence

In some embodimentexamples, the miRNA targeting sequence has complementarity to a miRNA that is endogenously expressed in a tissue in which expression of C1-INH is undesirable.

In some embodimentexamples, the patient is a mammal and the cells are mammalian cells.

In some embodimentexample, the mammal is a human and the cells are human cells.

In some embodimentexamples, the patient has a loss-of-function mutation in an endogenous gene encoding C1-INH. For example, the mutation may be a deletion or substitution of an amino acid located within the reactive center loop (RCL) of C1-INH. The mutation may be a deletion or substitution of K251. The mutation may be selected from the group consisting of A436T, R444H, R444C, R444S, V432E, A443V, Y199TER, I462S, and R378C.

In some embodimentexamples, the patient has a mutation in an endogenous gene encoding C1-INH that causes (i) a deletion or (ii) expression of a truncated transcript.

In some embodimentexamples, the patient has a mutation in a gene encoding coagulation factor XII (F12).

In some embodimentexamples, the mutation is heterozygous. In some embodimentexamples, the mutation is homozygous.

In some embodimentexamples, the patient has previously been treated with one or more immunosuppressive agents, biologic agents, and/or corticosteroids. In some embodimentexamples, the patient has not responded to treatment with the one or more immunosuppressive agents, biologic agents, and/or corticosteroids.

In some embodimentexamples, the patient has previously been treated with one or more therapeutic agents selected from the group consisting of C1-esterase inhibitor (e.g., BERINERT® or RUCONEST®), icatibant (e.g., icatibant injection, e.g., FIRAZYR®), and ecallantide (e.g., KALBITOR®). In some embodimentexamples, the patient has not responded to treatment with the one or more therapeutic agents.

In some embodimentexamples, the patient has previously been treated with one or more prophylactic agents selected from the group consisting of Cinryze, Haegarda, Takhzyro, and an androgen. In some embodimentexamples, the patient has not responded to treatment with the one or more prophylactic agents.

In some embodimentexamples, the patient is less than 12 years old (e.g., less than 6 years old). In some embodimentexamples, the patient is more than 6 years old (e.g., more than 12 years old).

In some embodimentexamples, 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.

In some embodimentexamples, 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.

In some embodimentexamples, after administering the population of pluripotent cells to the patient, the patient exhibits sustained disease remission.

In some embodimentexamples, 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.

In some embodimentexamples, 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 (e.g., from about 15 mg/dl to about 35 mg/dl).

In some embodimentexamples, 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 (i) is the same gender as the patient and/or (ii) has the same body mass index as the patient.

In some embodimentexamples, administration of the population of pluripotent cells to the patient reduces the patient's risk of suffocation due to laryngeal angioedema attacks.

In another aspectexample, the inventiondisclosure features a method of treating HAE in a patient in need thereof by administering to the patient a lentiviral vector including a transgene that encodes a C1-INH protein. In one aspect, the present disclosure refers to 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.

In another aspectexample, the inventiondisclosure features a method of inducing sustained remission of HAE in a patient in need thereof by administering to the patient a lentiviral vector including a transgene that encodes a C1-INH protein. In one aspect, the present disclosure refers to 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.

In another aspectexample, the inventiondisclosure features a method of preventing angioedema attacks in a patient diagnosed as having HAE by administering to the patient a lentiviral vector including a transgene that encodes a C1-INH protein. In one aspect, the present disclosure refers to 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.

In another aspectexample, the inventiondisclosure features a method of reducing the risk of recurrent angioedema attacks in a patient diagnosed as having HAE by administering to the patient a lentiviral vector including a transgene that encodes a C1-INH protein. In one aspect, the present disclosure refers to 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.

In some embodimentexamples, the angioedema attacks occur in the patient's skin, mucosa, gastrointestinal tract, and/or genitourinary region.

In another aspectexample, the inventiondisclosure features a method of reducing the risk of developing laryngeal angioedema attacks in a patient diagnosed as having HAE by administering to the patient a lentiviral vector including a transgene that encodes a C1-INH protein. In one aspect, the present disclosure refers to 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.

In some embodimentexamples, the lentiviral vector is administered systemically (e.g., via intravenous injection) to the patient.

In some embodimentexamples, the lentiviral vector includes 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.

In some embodimentexamples, the lentiviral vector is pseudotyped. The lentiviral vector may include 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.

In some [embodimentexamples](#), the lentiviral vector includes a VSV-G envelope protein.

In some [embodimentexamples](#), the transgene is operably linked to a ubiquitous promoter. In some [embodimentexamples](#), the transgene is operably linked to a tissue-specific promoter. In some [embodimentexamples](#), the transgene is operably linked to a hepatocyte-specific promoter.

In some [embodimentexamples](#), the transgene is operably linked to a transthyretin promoter, CD11b promoter, sp146/p47 promoter, CD68 promoter, sp146/gp9 promoter, EF1 α 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.

In some [embodimentexamples](#), the transgene is operably linked to an enhancer. The enhancer may include a β LCR.

In some [embodimentexamples](#), the transgene is operably linked to a miRNA targeting sequence

In some [embodimentexamples](#), the miRNA targeting sequence has complementarity to a miRNA that is endogenously expressed in a tissue in which expression of C1-INH is undesirable.

In some [embodimentexamples](#), the patient is a mammal (e.g., a human).

In some [embodimentexamples](#), the patient has a loss-of-function mutation in an endogenous gene encoding C1-INH. The mutation may be a deletion or a substitution of an amino acid located within the RCL of C1-INH. The mutation may be deletion or substitution of K251. The mutation may be selected from the group consisting of A436T, R444H, R444C, R444S, V432E, A443V, Y199TER, I462S, and R378C.

In some [embodimentexamples](#), the patient has a mutation in an endogenous gene encoding C1-INH that causes (i) a deletion or (ii) expression of a truncated transcript.

In some [embodimentexamples](#), the patient has a mutation in a gene encoding F12.

In some [embodimentexamples](#), the mutation is heterozygous. In some [embodimentexamples](#), the mutation is homozygous.

In some [embodimentexamples](#), the patient has previously been treated with one or more immunosuppressive agents, biologic agents, and/or corticosteroids. The patient may not have responded to treatment with the one or more immunosuppressive agents, biologic agents, and/or corticosteroids.

In some [embodimentexamples](#), the patient has previously been treated with one or more therapeutic agents selected from the group consisting of C1-esterase inhibitor (e.g., BERINERT® or RUCONEST®), icatibant (e.g., e.g., icatibant injection, e.g., FIRAZYR®), and ecallantide (e.g., KALBITOR®). The patient may not have responded to treatment with the one or more therapeutic agents.

In some [embodimentexamples](#), the patient has previously been treated with one or more prophylactic agents selected from the group consisting of Cinryze, Haegarda, Takhzyro, and an androgen. The patient may not have responded to treatment with the one or more prophylactic agents.

In some [embodimentexamples](#), the patient is less than 12 years old (e.g., less than 6 years old). In some [embodimentexamples](#), the patient is more than 6 years old (e.g., more than 12 years old).

In some embodimentexamples, 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.

In some embodimentexamples, prior to administering the lentiviral vector to the patient, the patient exhibits angioedema attacks with a frequency of one or two times per week.

In some embodimentexamples, after administering the lentiviral vector to the patient, the patient exhibits sustained disease remission.

In some embodimentexamples, 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.

In some embodimentexamples, 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 (e.g., from about 15 mg/dl to about 35 mg/dl).

In some embodimentexamples, 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 (i) is the same gender as the patient and/or (ii) has the same body mass index as the patient.

In some embodimentexamples, administration of the lentiviral vector to the patient reduces the patient's risk of suffocation due to laryngeal angioedema attacks.

In another aspectexample, the inventiondisclosure features a pharmaceutical composition that includes (i) a population of pluripotent cells including a transgene that encodes a C1-INH protein and (ii) one or more carriers, diluents, and/or excipients. In one aspect, the present disclosure refers to 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.

The cells may be human cells. The cells may be HSCs or HPCs. The cells may be embryonic stem cells. The cells may be induced pluripotent stem cells. The cells may be CD34+ cells (e.g., myeloid progenitor cells).

In some embodimentexamples, the composition is formulated for administration (e.g., via intravenous injection) to a human patient.

In some embodimentexamples, the cells are autologous with respect to the patient. In some embodimentexamples, the cells are allogeneic with respect to the patient. The cells may be HLA-matched to the patient.

In some embodimentexamples, the transgene is operably linked to a ubiquitous promoter. In some embodimentexamples, the transgene is operably linked to a tissue-specific promoter. In some embodimentexample, the transgene is operably linked to a myeloid cell-specific promoter.

In some embodimentexamples, the transgene is operably linked to a CD11b promoter, sp146/p47 promoter, CD68 promoter, sp146/gp9 promoter, EF1 α 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.

In some embodimentexamples, the transgene is operably linked to an enhancer. The enhancer may include a β LCR.

In some embodimentexamples, the transgene is operably linked to a miRNA targeting sequence. The miRNA targeting sequence may have complementarity to a miRNA that is endogenously expressed in a tissue in which expression of C1-INH is undesirable.

In another aspectexample, the inventiondisclosure features a pharmaceutical composition including (i) a lentiviral vector including a transgene that encodes a C1-INH protein and (ii) one or more carriers, diluents, and/or excipients. In one aspect, the present disclosure refers to 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.

In some embodimentexamples, the lentiviral vector includes 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.

In some embodimentexamples, the lentiviral vector is pseudotyped. The lentiviral vector may include 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. The lentiviral vector may include a VSV-G envelope protein.

In some embodimentexamples, the composition is formulated for administration (e.g., via intravenous injection) to a human patient.

In some embodimentexamples, the transgene is operably linked to a ubiquitous promoter. In some embodimentexamples, the transgene is operably linked to a tissue-specific promoter. In some embodimentexamples, the transgene is operably linked to a hepatocyte-specific promoter. The transgene may be operably linked to a transthyretin promoter, CD11b promoter, sp146/p47 promoter, CD68 promoter, sp146/gp9 promoter, EF1 α 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.

In some embodimentexamples, the transgene is operably linked to an enhancer. The transgene may include a β LCR.

In some embodimentexamples, the transgene is operably linked to a miRNA targeting sequence. The miRNA targeting sequence may have complementarity to a miRNA that is endogenously expressed in a tissue in which expression of C1-INH is undesirable.

In another aspectexample, the inventiondisclosure features a kit including a pharmaceutical composition as described herein. The kit may further include a package insert instructing a user of the kit to administer the pharmaceutical composition to a human patient having HAE. The package insert may instruct a user of the kit to perform a method as described herein. In one aspect, the present disclosure refers to a kit comprising the pharmaceutical composition as described herein, 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.

Definitions

As used herein, the terms “ablate,” “ablating,” “ablation,” “condition,” “conditioning,” and the like refer to the depletion of one or more cells in a population of cells in vivo or ex vivo. In some embodiments of the present disclosure, it may be desirable to ablate endogenous cells within a patient (e.g., a patient undergoing treatment for a disease described herein) before administering a therapeutic composition, such as a therapeutic population of cells, to the patient. This can be beneficial, for example, in order to provide newly-administered cells with an environment within which the cells may engraft. Ablation of a population of endogenous cells can be performed in a manner that selectively targets a specific cell type, for example, using antibodies or antibody-drug conjugates that bind to an antigen expressed on the target cell and subsequently engender the killing of the