

CLAIMS

1. A method of altering a nucleobase of a Fc fragment of IgG receptor and transporter (FcRn) polynucleotide, the method comprising contacting the FcRn polynucleotide with a base editor system comprising one or more guide polynucleotides and a base editor comprising a nucleic acid programmable DNA binding protein (napDNAbp) domain and a deaminase domain, or one or more polynucleotides encoding the base editor system, wherein

(a) the one or more guide polynucleotides comprises a nucleic acid sequence comprising at least 10-23 contiguous nucleotides of a spacer nucleic acid sequence listed in **Table 2B**; or

(b) said one or more guide polynucleotides targets said base editor to effect an alteration of a nucleobase in a codon encoding an amino acid residue selected from the group consisting of F110, L112, N113, E115, E116, F117, M118, N119, D121, L122, T126, W127, G128, D130, W131, P132, E133, A134, L135, and I137 relative to the following reference sequence:

FcRn amino acid sequence

AESHLSELLYHLTAVSSPAPGTPAFWVSGWLGPQQYLSYNSLRGEAEPGAWVWENQVSWYWEKE
TTDLRIKEKLFLEAFKALGGKGPYTLQGLLGCELGPDNTSVPTAKFALNGEEFMNFDLKQGTWG
GDWPEALAISQRWQQQDKAANKELTFLLFSCPHRLREHLERGRGNLEWKEPPSMRLKARPSSPG
FSVLTCSAFSFYPPELQLRFLRNGLAAGTGQGDGFPNSDGSFHASSSLTVKSGDEHHYCCIVQH
AGLAQPLRVELESPAKSSVLVVGIVIGVLLLTAAAVGGALLWRRMRSGLPAPWISLRGDDTGVL
LPTPGEAQDADLKDVNVIPATA (SEQ ID NO: 530), or a corresponding position in another
FcRn polypeptide sequence, thereby altering the nucleobase of the FcRn polynucleotide.

2. The method of claim 1, wherein the alteration of the nucleobase results in one or more of the following amino acid alterations in the FcRn polypeptide encoded by the FcRn polynucleotide relative to the reference sequence: F110L, F110S, F110P, L112P, N113S, N113D, E115G, E115K, E116G, E116K, E116Q, F117P, M118N, M118V, M118I, M118T, N119G, N119D, N119S, N119C, D121G, L122F, L122A, L122P, T126I, T126S, T126N, T126A, W127R, G128S, D130G, D130N, D130H, W131R, W131Q, P132L, P132S, P132P, E133G, A134V, L135P, I137V, I137T.

3. The method of claim 1, wherein the one or more guide polynucleotides target the base editor to effect an alteration of a nucleobase in a codon encoding the amino acid M118 or W131 in the reference sequence.
4. The method of any one of claims 2-3, wherein the one or more amino acid alterations in the FcRn polypeptide reduce or eliminate binding of the FcRn polypeptide to IgG1, IgG2, IgG3, and/or IgG4, and wherein the FcRn polypeptide comprising the one or more amino acid alterations has a K_D in solution for binding with IgG1, IgG2, IgG3, and/or IgG4 that is greater than 3000 nM.
5. The method of any one of claims 2-4, wherein the FcRn polypeptide encoded by the FcRn polynucleotide comprising an altered nucleobase is capable of binding albumin, and wherein the FcRn polypeptide comprising the one or more amino acid alterations has a K_D in solution for binding with albumin that is less than 2000 nM, less than 1000 nM, or less than 500 nM.
6. The method of any one of any one of claims 1-5, wherein the nucleobase of the FcRn polynucleotide is altered with a base editing efficiency of at least about 20%, at least about 40%, or at least about 50%.
7. The method of any one of claims 1-6, wherein the deaminase domain is an adenosine deaminase domain or a cytidine deaminase domain, and wherein the adenosine deaminase converts a target A•T to G•C in the FcRn polynucleotide and the cytidine deaminase converts a target C•G to T•A in the FcRn polynucleotide.
8. The method of claim 16, wherein the cytidine deaminase domain is an APOBEC deaminase domain or a derivative thereof, and the adenosine deaminase domain is a TadA deaminase domain.
9. The method of any one of claims 1-7, wherein the base editor is a BE4 base editor.

10. The method of claim 8, wherein the adenosine deaminase is a TadA*8.1, TadA*8.2, TadA*8.3, TadA*8.4, TadA*8.5, TadA*8.6, TadA*8.7, TadA*8.8, TadA*8.9, TadA*8.10, TadA*8.11, TadA*8.12, TadA*8.13, TadA*8.14, TadA*8.15, TadA*8.16, TadA*8.17, TadA*8.18, TadA*8.19, TadA*8.20, TadA*8.21, TadA*8.22, TadA*8.23, or TadA*8.24, or Tad*9 variant.
11. The method of any one of claims 1-10, wherein the napDNAbp domain comprises a Cas9, Cas12, Cas12a/Cpf1, Cas12b/C2cl, Cas12c/C2c3, Cas12d/CasY, Cas12e/CasX, Cas12g, Cas12h, Cas12i, or Cas12j/CasΦ polynucleotide or a functional portion thereof.
12. The method of any one of claims 1-11, wherein the napDNAbp domain comprises a nuclease active Cas9, a dead Cas9 (dCas9), or a Cas9 nickase (nCas9).
13. The method of any one of claims 1-12, wherein the napDNAbp domain is a *Staphylococcus aureus* Cas9 (SaCas9), *Streptococcus thermophilus* 1 Cas9 (St1Cas9), a *Streptococcus pyogenes* Cas9 (SpCas9), or variants thereof.
14. The method of claim 13, wherein the napDNAbp domain comprises a variant of SpCas9 or SaCas9 having an altered protospacer-adjacent motif (PAM) specificity.
15. The method of claim 14, wherein the SpCas9 or SaCas9 has specificity for a PAM sequence selected from the group consisting of NGG, NGA, NGC, NNGRRT, and NNNRRT, where N is any nucleotide and R is A or G.
16. The method of any one of claims 1-15, wherein the base editor further comprises one or more uracil glycosylase inhibitors (UGIs), or wherein the method further comprises expressing a UGI in a cell in trans with the base editor.
17. The method of any one of claims 1-16, wherein the base editor further comprises one or more nuclear localization signals (NLS).

18. The method of any one of claims 1-17, wherein the one or more guide polynucleotides comprise a scaffold comprising one of the following nucleotide sequences:
GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCA
CCGAGUCGGUGCUUUU (SpCas9 scaffold; SEQ ID NO: 317) or
GUUUUAGUACUCUGUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAUGCCGUGUUUAUC
UCGUCAACUUGUUGGCGAGAUUUU (SaCas9 scaffold; SEQ ID NO: 436).
19. The method of any one of claims 1-18, wherein the one or more guide polynucleotides comprise one or more modified nucleotides.
20. The method of claim 19, wherein the one or more guide polynucleotides comprise one or more modified polynucleotides, and wherein:
the one or more modified polynucleotides are at the 5' terminus and/or the 3' terminus of the one or more guide polynucleotides; and /or
the one or more modified nucleotides are 2'-O-methyl-3'-phosphorothioate nucleotides.
21. The method of any one of claims 1-20, wherein the one or more guide polynucleotides comprise a spacer consisting of from 19 to 23 nucleotides.
22. The method of any one of claims 1-21, wherein the FcRn polynucleotide is in a hepatocyte, an endothelial cell, a myeloid cell, or an epithelial cell.
23. A base editor system for altering a nucleobase of a Fc fragment of IgG receptor and transporter (FcRn) polynucleotide, the base editor system comprising: (i) one or more guide polynucleotides, or one or more polynucleotides encoding the one or more guide polynucleotides, and (ii) a base editor comprising a nucleic acid programmable DNA binding protein (napDNAbp) domain and a deaminase domain, or one or more polynucleotides encoding the base editor, wherein
(a) the one or more guide polynucleotides comprises a nucleic acid sequence comprising at least 10-23 contiguous nucleotides of a spacer nucleic acid sequence listed in **Table 2B**; or

(b) said one or more guide polynucleotides targets said base editor to effect an alteration of a nucleobase in a codon encoding an amino acid residue selected from the group consisting of F110, L112, N113, E115, E116, F117, M118, N119, D121, L122, T126, W127, G128, D130, W131, P132, E133, A134, L135, and I137 relative to the following reference sequence:

FcRn amino acid sequence

AESHLSELLYHLTAVSSPAPGTPAFWVSGWLGPQQYLSYNSLRGEAEPGAWVWENQVSWYWEKE
TTDLRIKEKLFLEAFKALGGKGPYTLQGLLGCELGPDNTSVPTAKFALNGEEFMNFDLKQGTWG
GDWPEALAISQRWQQQDKAANKELTFLFSCPHRLREHLERGRGNLEWKEPPSMRLKARPSSPG
FSVLTCSAFSFYPPELQLRFLRNGLAAGTGQGDFGPNSDGSFHASSSLTVKSGDEHHYCCIVQH
AGLAQPLRVELESPAKSSVLVVGIVIGVLLLTAAAVGGALLWRRMRSGLPAPWISLRGDDTGVL
LPTPGEAQDADLKDVNVIPATA (SEQ ID NO: 530), or a corresponding position in another
FcRn polypeptide sequence.

24. The base editor system of claim 23, wherein the alteration of the nucleobase results in one or more of the following amino acid alterations in the FcRn polypeptide encoded by the FcRn polynucleotide relative to the reference sequence: F110L, F110S, F110P, L112P, N113S, N113D, E115G, E115K, E116G, E116K, E116Q, F117P, M118N, M118V, M118I, M118T, N119G, N119D, N119S, N119C, D121G, L122F, L122A, L122P, T126I, T126S, T126N, T126A, W127R, G128S, D130G, D130N, D130H, W131R, W131Q, P132L, P132S, P132P, E133G, A134V, L135P, I137V, I137T.

25. The base editor system of claim 23, wherein the one or more guide polynucleotides target the base editor to effect an alteration of a nucleobase in a codon encoding the amino acid M118 or W131 in the reference sequence.

26. The base editor system of claim 25, wherein the alteration of the nucleobase results in an amino acid alteration in the FcRn polypeptide encoded by the FcRn polynucleotide selected from the group consisting of M118V, M118V, M118I, M118T, W131R, and W131Q.

27. The base editor system of any one of claims 24-26, wherein the one or more amino acid alterations in the FcRn polypeptide reduce or eliminate binding of the FcRn polypeptide to IgG1, IgG2, IgG3, and/or IgG4.
28. The base editor system of claim 23, wherein the FcRn polypeptide encoded by the FcRn polynucleotide comprising an altered nucleobase is capable of binding albumin.
29. The base editor system of claim 23, wherein the one or more guide polynucleotides comprise one or more modified nucleotides.
30. A vector comprising the polynucleotide of claim 1, wherein the vector is a viral vector, and the viral vector is a retroviral vector or an adeno-associated virus vector.
31. Use of a base editor system comprising one or more guide polynucleotides and a base editor comprising a nucleic acid programmable DNA binding protein (napDNAbp) domain and a deaminase domain, or one or more polynucleotides encoding the base editor system in the manufacture of a medicament for treating an autoimmune disorder mediated by immunoglobulin G (IgG) in a subject in need thereof, wherein:
- (a) the one or more guide polynucleotides comprises a nucleic acid sequence comprising at least 10-23 contiguous nucleotides of a spacer nucleic acid sequence listed in **Table 2B**; or
- (b) said one or more guide polynucleotides targets said base editor to effect an alteration of a nucleobase in a codon encoding an amino acid residue selected from the group consisting of F110, L112, N113, E115, E116, F117, M118, N119, D121, L122, T126, W127, G128, D130, W131, P132, E133, A134, L135, and I137 relative to the following reference sequence:
- FcRn amino acid sequence
- AESHLSELLYHLTAVSSPAPGTPAFWVSGWLGPQQYLSYNSLRGEAEPGAWWENQVSWYWEKE
TTDLRIKEKLFLEAFKALGGKGPYTLQGLLGCELGPDNTSVPTAKFALNGEEFMNFDLKQGTWG
GDWPEALAISQRWQQQDKAANKELTFLLFSCPHRLREHLERGRGNLEWKEPPSMRLKARPSSPG
FSVLTCSAFSFPPELQLRFLRNGLAAGTGQDGFPSDGSFHASSSLTVKSGDEHHYCCIVQH
AGLAQPLRVELESPAKSSVLVVGIVIGVLLLTAAAVGGALLWRRMRSGLPAPWISLRGDDTGVL
LPTPGEAQDADLKDVNVIPATA (SEQ ID NO: 436), or a corresponding position in another

FcRn polypeptide sequence by altering the nucleobase, thereby treating the autoimmune disorder.

32. The use of claim 31, wherein the alteration of the nucleobase results in one or more of the following amino acid alterations in the FcRn polypeptide encoded by the FcRn polynucleotide relative to the reference sequence: F110L, F110S, F110P, L112P, N113S, N113D, E115G, E115K, E116G, E116K, E116Q, F117P, M118N, M118V, M118I, M118T, N119G, N119D, N119S, N119C, D121G, L122F, L122A, L122P, T126I, T126S, T126N, T126A, W127R, G128S, D130G, D130N, D130H, W131R, W131Q, P132L, P132S, P132P, E133G, A134V, L135P, I137V, I137T.

33. The use of claim 31, wherein the one or more guide polynucleotides target the base editor to effect an alteration of a nucleobase in a codon encoding the amino acid M118 or W131 in the reference sequence.

34. The use of claim 33, wherein the alteration of the nucleobase results in an amino acid alteration in the FcRn polypeptide encoded by the FcRn polynucleotide selected from the group consisting of M118V, M118V, M118I, M118T, W131R, and W131Q.

35. The use of claim 31, wherein the use comprises decreasing levels of immunoglobulin G (IgG) polypeptides in the subject by at least about 25%; at least about 50%; or at least about 70%.

36. The use of claim 31, wherein the disorder is selected from the group consisting of myasthenia gravis (gMG), warm autoimmune hemolytic anemia (wAIHA), idiopathic thrombocytopenia purpura (ITP), Grave's disease, chronic inflammatory demyelinating polyneuropathy (CIDP), pemphigus vulgaris, and hemolytic diseases of fetus and newborn (HDFN).

37. The method of claim 1, wherein one or more of the guide polynucleotides comprises a sequence listed in **Table 2A** or **Table 2B**.

38. A method of altering a nucleobase of a Fc fragment of IgG receptor and transporter (FcRn) polynucleotide, the method comprising contacting the FcRn polynucleotide with a base editor system comprising one or more guide polynucleotides selected from the group consisting of gRNA1583, gRNA1578, gRNA3265, or one or more polynucleotides encoding the same, and a base editor comprising a nucleic acid programmable DNA binding protein (napDNAbp) domain and an adenosine deaminase domain, or one or more polynucleotides encoding the base editor; thereby altering the nucleobase of the FcRn polynucleotide.

39. A base editor system comprising one or more guide polynucleotides selected from the group consisting of gRNA1583, gRNA1578, gRNA3265, or one or more polynucleotides encoding the same, and a base editor comprising a nucleic acid programmable DNA binding protein (napDNAbp) domain and an adenosine deaminase domain, or one or more polynucleotides encoding the base editor.

40. A guide polynucleotide comprising a sequence listed in **Table 2A** or **Table 2B**.

41. A method of modifying a neonatal fragment crystallizable receptor (FcRn) protein in a mammalian cell, the method comprising contacting the cell with a guide RNA and a genome editor, wherein the guide RNA comprises a nucleotide sequence that is complementary to a portion of an *FCGRT* gene and targets the genome editor to effect a modification in the *FCGRT* gene in the cell, wherein the modification alters the amino acid sequence of the FcRn protein encoded by the *FCGRT* gene.

42. The method according to claim 41, wherein the genome editor comprises a base editor or a prime editor.

43. The method according to claim 42, wherein the base editor or prime editor is delivered to the mammalian cell via a nanoparticle, a viral vector, or electroporation.

44. The method according to claim 43, wherein the viral vector is selected from a retrovirus, an adenovirus, an adeno-associated virus (AAV), a herpesvirus, or a sendai virus.
45. The method according to any of claims 41-44, wherein the contacted cell expresses a variant FcRn protein comprising at least one amino acid alteration relative to a reference FcRn protein.
46. The method according to any of claims 41-45, wherein the genome editor is a prime editor comprising a nucleic acid programmable DNA binding domain and a reverse transcriptase and the guide RNA is a prime editing guide RNA (pegRNA), wherein the prime editor replaces one or more nucleotides in the *FCGRT* gene with a different nucleotide.
47. The method according to any of the preceding claims, wherein the modified FcRn protein differs from a reference FcRn protein at one or more amino acids selected from the group consisting of: leucine (L) at position 112, glutamic acid (E) at position 115, glutamic acid (E) at position 116, tryptophan (W) at position 131, proline (P) at position 132, and glutamic acid (E) at position 133.
48. The method according to claim 41, wherein the targeting moiety is selected from the group consisting of an Fc domain of IgG, an antibody that specifically binds FcRn, an antibody that specifically binds albumin, a peptide that binds albumin, albumin, or a fragment or derivative thereof.
49. A composition comprising a guide RNA and a genome editor, wherein the guide RNA comprises a nucleotide sequence that is complementary to a portion of the *FCGRT* gene and targets the base genome editor to effect a modification in the *FCGRT* gene in the cell, wherein the modification alters the amino acid sequence of the FcRn protein encoded by the *FCGRT* gene.
50. A method or composition according to any of the preceding claims, wherein the alteration of FcRn does not interfere with albumin half-life.