

CLAIMS

1. 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

AESHLSELLYHLTAVSSPAPGTPAFWVSGWLGPQQYLSYNSLRGEAEPGAWWENQVSWYWEKE
TTDLRIKEKLFLEAFKALGGKGPYTLQGLLGCELGPDNTSVPTAKFALNGEEFMNFDLKQGTWG
GDWPEALAIISQRWQQDKAANKELTFLLFSCPHRLREHLERGRGNLEWKEPPSMRLKARPSSPG
FSVLTCSAFSFPPELQLRFLRNGLAAGTGQGDFGPNSDGSFHASSSLTVKSGDEHHYCCIVQH
AGLAQPLRVELESPAKSSVLVVGIVIGVLLLLTAAVGGALLWRRMRSGLPAPWISLRGDDTGVL
LPTPGEAQDADLKDVNVIPATA (SEQ ID NO: 530), or a corresponding position in another
FcRn polypeptide sequence.

2. The base editor system 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 base editor system 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 base editor system of claim 3, 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.
5. The base editor system of any one of claims 2-4, 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.
6. The base editor system of claim 1, wherein the FcRn polypeptide encoded by the FcRn polynucleotide comprising an altered nucleobase is capable of binding albumin.
7. The base editor system of claim 1, wherein the one or more guide polynucleotides comprise one or more modified nucleotides.
8. A vector comprising a polynucleotide encoding the base editor system of claim 1, wherein the vector is a viral vector, and the viral vector is a retroviral vector or an adeno-associated virus vector.
9. 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

AESHLSELLYHLTAVSSPAPGTPAFWVSGWLGPPQYLSYNSLRGEAEPCGAWWENQVSWYWEKE
TTDLRIKEKLFLEAFKALGGKGPYTLQGLLGCELGPDNTSVPTAKFALNGEEFMNFDLKQGTWG
GDWPEALAISQRWQQDKAANKELTFLLFSCPHRLREHLERGRGNLEWKEPPSMRLKARPSSPG
FSVLTCSAFSFYPPELQLRFLRNGLAAGTGQGDFGPNSDGSFHASSSLTVKSGDEHHYCCIVQH
AGLAQPLRVELESPAKSSVLVVGIVIGVLLLLTAAVGGALLWRRMRSGLPAPWISLRGDDTGVL
LPTPGEAQDADLKDVNVIPATA (SEQ ID NO: 436), or a corresponding position in another
FcRn polypeptide sequence by altering the nucleobase, thereby treating the autoimmune
disorder.

10. The use of claim 9, 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.

11. The use of claim 9, wherein the one or more guide polynucleotides target the base editor to affect an alteration of a nucleobase in a codon encoding the amino acid M118 or W131 in the reference sequence.

12. The use of claim 11, 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.

13. The use of claim 9, wherein the use comprises decreasing levels of immunoglobulin G (IgG) polypeptides in the subject by at least 25%; at least 50%; or at least 70%.

14. The use of claim 9, 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).

15. 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.