CLAIMS

1. A base editor system comprising one or more guide RNAs, or one or more polynucleotides encoding the one or more guide RNAs, 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, for use in contacting a complement component (C3) polynucleotide to alter a nucleobase of the C3 polynucleotide; wherein:

(a) said one or more guide RNAs targets said base editor to effect an alteration of a nucleobase of the C3 polynucleotide that disrupts a splice site in the C3 polynucleotide;

(b) the deaminase domain is a TadA variant (TadA*) comprising a combination of alterations listed in **Table 5A, 5B, 5C, 5D, 5E, 6A, 6B, 6C, 6D, 6E, 6F, or 7**, wherein the TadA* is not TadA*7.9 or TadA*7.10, and/or wherein the TadA* variant is a TadA*8.8, TadA*8.17, or TadA*8.20 variant comprising one or more of the amino acid alterations V82T, Y147T, and Q154S;

(c) the one or more guide RNAs comprises a nucleic acid sequence comprising at least 10-23 contiguous nucleotides of a spacer nucleic acid sequence listed in any one of **Tables 1A, 1B, 1C, 1D, 1E, 1F, and 2**;

(d) said one or more guide RNAs 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 A741, S742, H743, A747, L746, R748, S749, I1125, H1126, Q1127, and E1128 relative to the following reference sequence:

C3 amino acid sequence

MGPTSGPSLLLLLLTHLPLALGSPMYSIITPNILRLESEETMVLEAHDAQGDVPVTVTVHDF
PGKKLVLSSEKTVLTPATNHMGNVTFTIPANREFKSEKGRNKFVTVQATFGTQVVEKVVLVS
LQSGYLFIQTDKTIYTPGSTVLYRIFTVNHKLLPVGRTVMVNIENPEGIPVKQDSLSSQNQL
GVLPLSWDIPELVNMGQWKIRAYYENSPQQVFSTEFEVKEYVLPSFEVIVEPTEKFYYIYNE
KGLEVTITARFLYGKKVEGTAFVIFGIQDGEQRISLPESLKRIPIEDGSGEVVLSRKVLLDG
VQNPRAEDLVGKSLYVSATVILHSGSDMVQAERSGIPIVTSPYQIHFTKTPKYFKPGMPFDL
MVFVTNPDGSPAYRVPVAVQGEDTVQSLTQGDGVAKLSINTHPSQKPLSITVRTKKQELSEA
EQATRTMQALPYSTVGNSNNYLHLSVLRTELRPGETLNVNFLLRMDRAHEAKIRYYTYLIMN
KGRLLKAGRQVREPGQDLVVLPLSITTDFIPSFRLVAYYTLIGASGQREVVADSVWVDVKDS
CVGSLVVKSGQSEDRQPVPGQQMTLKIEGDHGARVVLVAVDKGVFVLNKKNKLTQSKIWDVV
EKADIGCTPGSGKDYAGVFSDAGLTFTSSSGQQTAQRAELQCPQPAARRRRSVQLTEKRMDK

VGKYPKELRKCCEDGMRENPMRFSCQRRTRFISLGEACKKVFLDCCNYITELRRQHARASHL
GLARSNLDEDIIAEENIVSRSEFPESWLWNVEDLKEPPKNGISTKLMNIFLKDSITTWEILA
VSMSDKKGICVADPFEVTVMQDFFIDLRLPYSVVRNEQVEIRAVLYNYRQNQELKVRVELLH
NPAFCSLATTKRRHQQTVTIPPKSSLSVPYVIVPLKTGLQEVEVKAAVYHHFISDGVRKSLK
VVPEGIRMNKTVAVRTLDPERLGREGVQKEDIPPADLSDQVPDTESETRILLQGTPVAQMTE
DAVDAERLKHLIVTPSGCGEQNMIGMTPTVIAVHYLDETEQWEKFGLEKRQGALELIKKGYT
QQLAFRQPSSAFAAFVKRAPSTWLTAYVVKVFSLAVNLIAIDSQVLCGAVKWLILEKQKPDG
VFQEDAPVIHQEMIGGLRNNNEKDMALTAFVLISLQEAKDICEEQVNSLPGSITKAGDFLEA
NYMNLQRSYTVAIAGYALAQMGRLKGPLLNKFLTTAKDKNRWEDPGKQLYNVEATSYALLAL
LQLKDFDFVPPVVRWLNEQRYYGGGYGSTQATFMVFQALAQYQKDAPDHQELNLDVSLQLPS
RSSKITHRIHWESASLLRSEETKENEGFTVTAEGKGQGTLSVVTMYHAKAKDQLTCNKFDLK
VTIKPAPETEKRPQDAKNTMILEICTRYRGDQDATMSILDISMMTGFAPDTDDLKQLANGVD
RYISKYELDKAFSDRNTLIIYLDKVSHSEDDCLAFKVHQYFNVELIQPGAVKVYAYYNLEES
CTRFYHPEKEDGKLNKLCRDELCRCAEENCFIQKSDDKVTLEERLDKACEPGVDYVYKTRLV
KVQLSNDFDEYIMAIEQTIKSGSDEVQVGQQRTFISPIKCREALKLEEKKHYLMWGLSSDFW
GEKPNLSYIIGKDTWVEHWPEEDECQDEENQKQCQDLGAFTESMVVFGCPN (SEQ ID NO: 796), or a corresponding position in another C3 polypeptide sequence; or

(e) said one or more guide RNAs targets said base editor to effect an alteration of a nucleobase in a start codon of the C3 polynucleotide.

2. The base editor system for the use of claim 1, wherein:

(a) the splice site corresponds to any one of the protospacers listed in **Table 1A, 1B, or 1C**; or

(b) the deaminase is an adenosine deaminase selected from the group consisting of TadA*8.8, TadA*8.13, TadA*8.17, TadA*8.20, TadA*8.8_V82T, TadA*8.8_V82T_Y147T_Q154S, TadA*8.17_V82T, TadA*8.17_V82T_Y147T_Q154S, TadA*8.20_V82T, and TadA*8.20_V82T_Y147T_Q154S; or

(c) the base editor is selected from the group consisting of ABE8.8, ABE8.13, ABE8.17, ABE8.20, ABE8.8_V82T, ABE8.8_V82T_Y147T_Q154S, ABE8.17_V82T, ABE8.17_V82T_Y147T_Q154S, ABE8.20_V82T, ABE8.20_V82T_Y147T_Q154S, BE4, and those base editors listed in **Tables 1A, 1B, 1C, 1D, 1E, 1F, 2, and 8-15**; or

(d) the one or more guide RNAs comprise a spacer consisting of from about 19 to about 23 nucleotides, in particular wherein the spacer consists of 21 nucleotides; or

(e) the one or more guide RNAs comprise a spacer corresponding to a guide polynucleotide selected from the group consisting of gRNA676, gRNA661, gRNA715, gRNA821, gRNA837, gRNA838, gRNA827, gRNA828, gRNA829, gRNA3342, gRNA3343, and gRNA3345.

3. One or more guide RNAs, or one or more polynucleotides encoding the one or more guide RNAs, 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; for use in contacting a complement component (C3) polynucleotide to alter a nucleobase of the C3 polynucleotide; wherein:

(a) the deaminase domain is selected from the group consisting of TadA*8.8, TadA*8.13, TadA*8.17, TadA*8.20, TadA*8.8_V82T, TadA*8.8_V82T_Y147T_Q154S, TadA*8.17_V82T, TadA*8.17_V82T_Y147T_Q154S, TadA*8.20_V82T, TadA*8.20_V82T_Y147T_Q154S, rAPOBEC1, and ppAPOBEC; and

(b) the one or more guide RNAs comprise a spacer corresponding to a guide polynucleotide selected from the group consisting of gRNA661, gRNA662, gRNA676, gRNA695, gRNA696, gRNA701, gRNA715, gRNA821, gRNA837, gRNA838, gRNA827, gRNA828, gRNA829, gRNA1793, gRNA1798, gRNA3342, gRNA3343, and gRNA3345.

4. The base editor system for the use of claim 1 or claim 2; or the one or more guide RNAs, or one or more polynucleotides encoding the one or more guide RNAs, and a base editor, or one or more polynucleotides encoding the base editor; for the use of claim 3, wherein the napDNAbp domain comprises a Cas9 variant, in particular wherein

(a) the Cas9 variant comprises one or more of the amino acid alterations A1283D and E1250K relative to an SpCas9 reference amino acid sequence; or

(b) the Cas9 variant comprises one or more of the following combinations of amino acid alterations relative to an spCas9 reference amino acid sequence:
I322V, S409I, E427G, R654L, R753G, and R1114G;
I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, and R1337K;
I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, R1337K, and A1283D;
I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, R1337K, A1283D, R220A, and R221A;
I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, R1337K, A1283D, R765A, and Q768A;

I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, R1337K, A1283D, R765A, Q768A, K772A, and K775A;
I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, R1337K, A1283D, and E1250K;
I322V, S409I, E427G, R654L, R753G, R1114G, Q1136Y, A1283D, and E1250K;
I322V, S409I, E427G, R654L, R753G, R1114G, Q1136Y, and R1337K; and
I322V, S409I, E427G, R654L, R753G, R1114G, and R1337K; or. (c) the Cas9 variant is a SaCas9-KHH, SpCas9-MQKFRAER, or SpCas9-VRQR.

5. The base editor system or the one or more guide RNAs, or one or more polynucleotides encoding the one or more guide RNAs, and a base editor, or one or more polynucleotides encoding the base editor; for the use of any one of claims 1-4, wherein:
(a) the one or more guide RNAs comprises a nucleic acid analog, in particular wherein the one or more guide RNAs comprise one or more of a 2′-OMe and a phosphorothioate, more in particular wherein the one or more guide RNAs comprise one of the following nucleotide sequences:
End-mod SpCas9 guide polynucleotide:
mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO: 943);
End-mod SaCas9 guide polynucleotide:
mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGUACUCUGUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU (SEQ ID NO: 944);
H M01:
mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 855);
H M07:
mNsmNsmNsmNmNmNmNmNmNmNNNNNNNNNNNNmGUUUUAGmAmGmCmUmAmGmAmAmAmUmAmGmCmAmAGUUmAAmAAmUAmAmGmGmCmUmAGUmCmCGUUAmUmCAAmCmUmUmGmAmAmAmAmGmUmGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 856);
NLS (bpsv 40):
mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU

AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU (SEQ ID NOs: 857);

LONG EST:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGUGmG mCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 859);

NLS + LONG ST :

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmG mGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NOs: 860); or

LONGEST + G OLD:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAmUmCAAmCmUmUGGACUUCGGUCCmAmAm GUGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 861);

wherein "mN" indicates a 2′-OMe modification of the nucleotide "N", and "Ns" indicates that the nucleotide "N" is linked to the following nucleotide by a phosphorothioate (PS), more in particular wherein one or more or the one or more guide RNAs are covalently linked at the 5' end to a peptide having the following amino acid sequence: CKRTADGSEFESPKKKRKV (SEQ ID NO: 858) or

(b) the base editor comprises a linker peptide between the deaminase domain and the napDNAbp domain, wherein the linker peptide comprises the amino acid sequence KGPKPKKEESEK (SEQ ID NO: 940); or

(c) the nucleobase alteration effects an alteration to an encoded amino acid residue, wherein the alteration disrupts opsonization by C3; or

(d) the nucleobase alteration disrupts splicing of a C3 transcript; or

(e) the nucleobase alteration effects an alteration to an encoded amino acid residue, wherein the alteration disrupts cleavage of the C3 polypeptide by a C3 convertase or

(f) said one or more guide RNAs 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 A741, S742, H743, A747, L746, R748, S749, I1125, H1126, Q1127, and E1128 relative to the following reference sequence:

C3 amino acid sequence

MGPTSGPSLLLLLLTHLPLALGSPMYSIITPNILRLESEETMVLEAHDAQGDVPVTVTVHDF
PGKKLVLSSEKTVLTPATNHMGNVTFTIPANREFKSEKGRNKFVTVQATFGTQVVEKVVLVS
LQSGYLFIQTDKTIYTPGSTVLYRIFTVNHKLLPVGRTVMVNIENPEGIPVKQDSLSSQNQL
GVLPLSWDIPELVNMGQWKIRAYYENSPQQVFSTEFEVKEYVLPSFEVIVEPTEKFYYIYNE
KGLEVTITARFLYGKKVEGTAFVIFGIQDGEQRISLPESLKRIPIEDGSGEVVLSRKVLLDG
VQNPRAEDLVGKSLYVSATVILHSGSDMVQAERSGIPIVTSPYQIHFTKTPKYFKPGMPFDL
MVFVTNPDGSPAYRVPVAVQGEDTVQSLTQGDGVAKLSINTHPSQKPLSITVRTKKQELSEA
EQATRTMQALPYSTVGNSNNYLHLSVLRTELRPGETLNVNFLLRMDRAHEAKIRYYTYLIMN
KGRLLKAGRQVREPGQDLVVLPLSITTDFIPSFRLVAYYTLIGASGQREVVADSVWVDVKDS
CVGSLVVKSGQSEDRQPVPGQQMTLKIEGDHGARVVLVAVDKGVFVLNKKNKLTQSKIWDVV
EKADIGCTPGSGKDYAGVFSDAGLTFTSSSGQQTAQRAELQCPQPAARRRRSVQLTEKRMDK
VGKYPKELRKCCEDGMRENPMRFSCQRRTRFISLGEACKKVFLDCCNYITELRRQHARASHL
GLARSNLDEDIIAEENIVSRSEFPESWLWNVEDLKEPPKNGISTKLMNIFLKDSITTWEILA
VSMSDKKGICVADPFEVTVMQDFFIDLRLPYSVVRNEQVEIRAVLYNYRQNQELKVRVELLH
NPAFCSLATTKRRHQQTVTIPPKSSLSVPYVIVPLKTGLQEVEVKAAVYHHFISDGVRKSLK
VVPEGIRMNKTVAVRTLDPERLGREGVQKEDIPPADLSDQVPDTESETRILLQGTPVAQMTE
DAVDAERLKHLIVTPSGCGEQNMIGMTPTVIAVHYLDETEQWEKFGLEKRQGALELIKKGYT
QQLAFRQPSSAFAAFVKRAPSTWLTAYVVKVFSLAVNLIAIDSQVLCGAVKWLILEKQKPDG
VFQEDAPVIHQEMIGGLRNNNEKDMALTAFVLISLQEAKDICEEQVNSLPGSITKAGDFLEA
NYMNLQRSYTVAIAGYALAQMGRLKGPLLNKFLTTAKDKNRWEDPGKQLYNVEATSYALLAL
LQLKDFDFVPPVVRWLNEQRYYGGGYGSTQATFMVFQALAQYQKDAPDHQELNLDVSLQLPS
RSSKITHRIHWESASLLRSEETKENEGFTVTAEGKGQGTLSVVTMYHAKAKDQLTCNKFDLK
VTIKPAPETEKRPQDAKNTMILEICTRYRGDQDATMSILDISMMTGFAPDTDDLKQLANGVD
RYISKYELDKAFSDRNTLIIYLDKVSHSEDDCLAFKVHQYFNVELIQPGAVKVYAYYNLEES
CTRFYHPEKEDGKLNKLCRDELCRCAEENCFIQKSDDKVTLEERLDKACEPGVDYVYKTRLV
KVQLSNDFDEYIMAIEQTIKSGSDEVQVGQQRTFISPIKCREALKLEEKKHYLMWGLSSDFW
GEKPNLSYIIGKDTWVEHWPEEDECQDEENQKQCQDLGAFTESMVVFGCPN (SEQ ID NO: 796), in particular wherein the nucleobase alteration effects an alteration to an encoded amino acid residue selected from the group consisting of A741V, S742G, H743R, H743Y, A747V, A747T, L746P, R748G, R748K, S749G, C1010R, C1010Y, Q1013R, I1125M, H1126R, H1126Y, Q1127R, E1128G, and E1128K; or

(g) said one or more guide RNAs targets said base editor to effect an alteration of a nucleobase in a start codon of the C3 polynucleotide; or

(h) the editing rate for the base editor system is greater than 35%; or

(i) the C3 polynucleotide is in a cell of a mammal, in particular wherein the cell is a retinal cell or other cell of the eye, a cell of the CNS, or a hepatocyte.

6. One or more guide RNAs, or one or more polynucleotides encoding the one or more guide RNAs, 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; for use in altering a nucleobase of a complement component 3 (C3) polynucleotide to treat a disease or disorder associated with inappropriate inactivation of the complement system in a subject; wherein:

(a) said one or more guide RNAs targets said base editor to effect an alteration of the nucleobase of the C3 polynucleotide that disrupts a splice site in the C3 polynucleotide;

(b) the deaminase domain is a TadA variant (TadA*) comprising a combination of alterations listed in **Table 5A, 5B, 5C, 5D, 5E, 6A, 6B, 6C, 6D, 6E, 6F, or 7**, wherein the TadA* is not TadA*7.9 or TadA*7.10,

(c) the one or more guide RNAs comprise a nucleic acid sequence comprising at least 10-23 contiguous nucleotides of a spacer nucleic acid sequence listed in any one of **Tables 1A, 1B, 1C, 1D, 1E, 1F, and 2**; or

(d) said one or more guide RNAs 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 A741, S742, H743, A747, L746, R748, S749, I1125, H1126, Q1127, and E1128 relative to the following reference sequence:

C3 amino acid sequence

MGPTSGPSLLLLLLTHLPLALGSPMYSIITPNILRLESEETMVLEAHDAQGDVPVTVTVHDF
PGKKLVLSSEKTVLTPATNHMGNVTFTIPANREFKSEKGRNKFVTVQATFGTQVVEKVVLVS
LQSGYLFIQTDKTIYTPGSTVLYRIFTVNHKLLPVGRTVMVNIENPEGIPVKQDSLSSQNQL
GVLPLSWDIPELVNMGQWKIRAYYENSPQQVFSTEFEVKEYVLPSFEVIVEPTEKFYYIYNE
KGLEVTITARFLYGKKVEGTAFVIFGIQDGEQRISLPESLKRIPIEDGSGEVVLSRKVLLDG
VQNPRAEDLVGKSLYVSATVILHSGSDMVQAERSGIPIVTSPYQIHFTKTPKYFKPGMPFDL
MVFVTNPDGSPAYRVPVAVQGEDTVQSLTQGDGVAKLSINTHPSQKPLSITVRTKKQELSEA
EQATRTMQALPYSTVGNSNNYLHLSVLRTELRPGETLNVNFLLRMDRAHEAKIRYYTYLIMN
KGRLLKAGRQVREPGQDLVVLPLSITTDFIPSFRLVAYYTLIGASGQREVVADSVWVDVKDS
CVGSLVVKSGQSEDRQPVPGQQMTLKIEGDHGARVVLVAVDKGVFVLNKKNKLTQSKIWDVV
EKADIGCTPGSGKDYAGVFSDAGLTFTSSSGQQTAQRAELQCPQPAARRRRSVQLTEKRMDK
VGKYPKELRKCCEDGMRENPMRFSCQRRTRFISLGEACKKVFLDCCNYITELRRQHARASHL

GLARSNLDEDIIAEENIVSRSEFPESWLWNVEDLKEPPKNGISTKLMNIFLKDSITTWEILA
VSMSDKKGICVADPFEVTVMQDFFIDLRLPYSVVRNEQVEIRAVLYNYRQNQELKVRVELLH
NPAFCSLATTKRRHQQTVTIPPKSSLSVPYVIVPLKTGLQEVEVKAAVYHHFISDGVRKSLK
VVPEGIRMNKTVAVRTLDPERLGREGVQKEDIPPADLSDQVPDTESETRILLQGTPVAQMTE
DAVDAERLKHLIVTPSGCGEQNMIGMTPTVIAVHYLDETEQWEKFGLEKRQGALELIKKGYT
QQLAFRQPSSAFAAFVKRAPSTWLTAYVVKVFSLAVNLIAIDSQVLCGAVKWLILEKQKPDG
VFQEDAPVIHQEMIGGLRNNNEKDMALTAFVLISLQEAKDICEEQVNSLPGSITKAGDFLEA
NYMNLQRSYTVAIAGYALAQMGRLKGPLLNKFLTTAKDKNRWEDPGKQLYNVEATSYALLAL
LQLKDFDFVPPVVRWLNEQRYYGGGYGSTQATFMVFQALAQYQKDAPDHQELNLDVSLQLPS
RSSKITHRIHWESASLLRSEETKENEGFTVTAEGKGQGTLSVVTMYHAKAKDQLTCNKFDLK
VTIKPAPETEKRPQDAKNTMILEICTRYRGDQDATMSILDISMMTGFAPDTDDLKQLANGVD
RYISKYELDKAFSDRNTLIIYLDKVSHSEDDCLAFKVHQYFNVELIQPGAVKVYAYYNLEES
CTRFYHPEKEDGKLNKLCRDELCRCAEENCFIQKSDDKVTLEERLDKACEPGVDYVYKTRLV
KVQLSNDFDEYIMAIEQTIKSGSDEVQVGQQRTFISPIKCREALKLEEKKHYLMWGLSSDFW
GEKPNLSYIIGKDTWVEHWPEEDECQDEENQKQCQDLGAFTESMVVFGCPN (SEQ ID NO: 796), or a corresponding position in another C3 polypeptide sequence; or

(e) said one or more guide RNAs targets said base editor to effect an alteration of a nucleobase in a start codon of the C3 polynucleotide; or

(f)(1) the deaminase domain is selected from the group consisting of TadA*8.8, TadA*8.13, TadA*8.17, TadA*8.20, TadA*8.8_V82T, TadA*8.8_V82T_Y147T_Q154S, TadA*8.17_V82T, TadA*8.17_V82T_Y147T_Q154S, TadA*8.20_V82T, TadA*8.20_V82T_Y147T_Q154S, rAPOBEC1, and ppAPOBEC; and

(2) the one or more guide RNAs comprise a spacer corresponding to a guide polynucleotide selected from the group consisting of gRNA661, gRNA662, gRNA676, gRNA695, gRNA696, gRNA701, gRNA715, gRNA821, gRNA837, gRNA838, gRNA827, gRNA828, gRNA829, gRNA1793, gRNA1798, gRNA3342, gRNA3343, and gRNA3345.

7. The one or more guide RNAs, or one or more polynucleotides encoding the one or more guide RNAs, and the base editor, or one or more polynucleotides encoding the base editor; for the use of claim 6, wherein:

(a) the one or more guide RNAs target said base editor to effect an alteration of the nucleobase of a C3 polynucleotide that disrupts a splice site in the C3 polynucleotide, wherein the splice site is selected from the group consisting of those splice sites corresponding to any of the protospacers listed in **Table 1A, 1B, or 1C**; or

(b) the deaminase is an adenosine deaminase or a cytidine deaminase; or

(c) the deaminase is an adenosine deaminase selected from the group consisting of TadA*8.8, TadA*8.13, TadA*8.17, TadA*8.20, TadA*8.8_V82T, TadA*8.8_V82T_Y147T_Q154S, TadA*8.17_V82T, TadA*8.17_V82T_Y147T_Q154S, TadA*8.20_V82T, and TadA*8.20_V82T_Y147T_Q154S; or

(d) the base editor is selected from the group consisting of ABE8.8, ABE8.13, ABE8.17, ABE8.20, ABE8.8_V82T, ABE8.8_V82T_Y147T_Q154S, ABE8.17_V82T, ABE8.17_V82T_Y147T_Q154S, ABE8.20_V82T, ABE8.20_V82T_Y147T_Q154S, BE4, and those base editors listed in **Tables 1A, 1B, 1C, 1D, 1E, 1F, 2, and 8-15**; or

(e) the napDNAbp domain comprises a Cas9 variant, in particular wherein the Cas9 variant comprises one or more of the amino acid alterations A1283D and E1250K relative to an SpCas9 reference amino acid sequence, or wherein the Cas9 variant comprises one or more of the following combinations of amino acid alterations relative to an spCas9 reference amino acid sequence:

I322V, S409I, E427G, R654L, R753G, and R1114G;

I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, and R1337K;

I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, R1337K, and A1283D;

I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, R1337K, A1283D, R220A, and R221A;

I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, R1337K, A1283D, R765A, and Q768A;

I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, R1337K, A1283D, R765A, Q768A, K772A, and K775A;

I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, R1337K, A1283D, and E1250K;

I322V, S409I, E427G, R654L, R753G, R1114G, Q1136Y, A1283D, and E1250K;

I322V, S409I, E427G, R654L, R753G, R1114G, Q1136Y, and R1337K; and

I322V, S409I, E427G, R654L, R753G, R1114G, and R1337K, or wherein the Cas9 variant is a SaCas9-KHH, SpCas9-MQKFRAER, or SpCas9-VRQR; or

(f) said one or more guide RNAs 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 A741, S742, H743, A747, L746, R748, S749, I1125, H1126, Q1127, and E1128 relative to the following reference sequence:

C3 amino acid sequence

MGPTSGPSLLLLLLTHLPLALGSPMYSIITPNILRLESEETMVLEAHDAQGDVPVTVTVHDF
PGKKLVLSSEKTVLTPATNHMGNVTFTIPANREFKSEKGRNKFVTVQATFGTQVVEKVVLVS
LQSGYLFIQTDKTIYTPGSTVLYRIFTVNHKLLPVGRTVMVNIENPEGIPVKQDSLSSQNQL
GVLPLSWDIPELVNMGQWKIRAYYENSPQQVFSTEFEVKEYVLPSFEVIVEPTEKFYYIYNE
KGLEVTITARFLYGKKVEGTAFVIFGIQDGEQRISLPESLKRIPIEDGSGEVVLSRKVLLDG
VQNPRAEDLVGKSLYVSATVILHSGSDMVQAERSGIPIVTSPYQIHFTKTPKYFKPGMPFDL
MVFVTNPDGSPAYRVPVAVQGEDTVQSLTQGDGVAKLSINTHPSQKPLSITVRTKKQELSEA
EQATRTMQALPYSTVGNSNNYLHLSVLRTELRPGETLNVNFLLRMDRAHEAKIRYYTYLIMN
KGRLLKAGRQVREPGQDLVVLPLSITTDFIPSFRLVAYYTLIGASGQREVVADSVWVDVKDS
CVGSLVVKSGQSEDRQPVPGQQMTLKIEGDHGARVVLVAVDKGVFVLNKKNKLTQSKIWDVV
EKADIGCTPGSGKDYAGVFSDAGLTFTSSSGQQTAQRAELQCPQPAARRRRSVQLTEKRMDK
VGKYPKELRKCCEDGMRENPMRFSCQRRTRFISLGEACKKVFLDCCNYITELRRQHARASHL
GLARSNLDEDIIAEENIVSRSEFPESWLWNVEDLKEPPKNGISTKLMNIFLKDSITTWEILA
VSMSDKKGICVADPFEVTVMQDFFIDLRLPYSVVRNEQVEIRAVLYNYRQNQELKVRVELLH
NPAFCSLATTKRRHQQTVTIPPKSSLSVPYVIVPLKTGLQEVEVKAAVYHHFISDGVRKSLK
VVPEGIRMNKTVAVRTLDPERLGREGVQKEDIPPADLSDQVPDTESETRILLQGTPVAQMTE
DAVDAERLKHLIVTPSGCGEQNMIGMTPTVIAVHYLDETEQWEKFGLEKRQGALELIKKGYT
QQLAFRQPSSAFAAFVKRAPSTWLTAYVVKVFSLAVNLIAIDSQVLCGAVKWLILEKQKPDG
VFQEDAPVIHQEMIGGLRNNNEKDMALTAFVLISLQEAKDICEEQVNSLPGSITKAGDFLEA
NYMNLQRSYTVAIAGYALAQMGRLKGPLLNKFLTTAKDKNRWEDPGKQLYNVEATSYALLAL
LQLKDFDFVPPVVRWLNEQRYYGGGYGSTQATFMVFQALAQYQKDAPDHQELNLDVSLQLPS
RSSKITHRIHWESASLLRSEETKENEGFTVTAEGKGQGTLSVVTMYHAKAKDQLTCNKFDLK
VTIKPAPETEKRPQDAKNTMILEICTRYRGDQDATMSILDISMMTGFAPDTDDLKQLANGVD
RYISKYELDKAFSDRNTLIIYLDKVSHSEDDCLAFKVHQYFNVELIQPGAVKVYAYYNLEES
CTRFYHPEKEDGKLNKLCRDELCRCAEENCFIQKSDDKVTLEERLDKACEPGVDYVYKTRLV
KVQLSNDFDEYIMAIEQTIKSGSDEVQVGQQRTFISPIKCREALKLEEKKHYLMWGLSSDFW
GEKPNLSYIIGKDTWVEHWPEEDECQDEENQKQCQDLGAFTESMVVFGCPN (SEQ ID NO: 796), in particular wherein the nucleobase alteration effects an alteration to an encoded amino acid residue selected from the group consisting of A741V, S742G, H743R, H743Y, A747V, A747T, L746P, R748G, R748K, S749G, C1010R, C1010Y, Q1013R, I1125M, H1126R, H1126Y Q1127R, E1128G, and E1128K; or

(g) the one or more guide RNAs comprise a nucleic acid analog,, in particular wherein the one or more guide RNAs comprise one or more of a 2′-OMe and a phosphorothioate,

more in particular wherein the one or more guide RNAs comprise one of the following nucleotide sequences:

End-mod SpCas9 guide polynucleotide:

mNsmNsmNsNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU

AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO: 943);

End-mod SaCas9 guide polynucleotide:

mNsmNsmNsNNNNNNNNNNNNNNNNNNGUUUUAGUACUCUGUAAUGAAAAUUACAGAAUCUA

CUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU

(SEQ ID NO: 944);

HM01:

mNsmNsmNsNNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGU

UAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmG

mAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 855);

HM07:

mNsmNsmNsmNmNmNmNmNmNNNNNNNNNNNmGUUUUAGmAmGmCmUmAmGmAmAmAmUm

AmGmCmAmAGUUmAAmAAmUAmAmGmGmCmUmAGUmCmCGUUAmUmCAAmCmUmUmGmAmAm

AmAmAmGmUmGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 856);

NLS (bpsv40):

mNsmNsmNsNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU

AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU (SEQ ID NOs: 857);

LONGEST:

mNsmNsmNsNNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC

mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGUGmG

mCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 859);

NLS + LONGEST:

mNsmNsmNsNNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC

mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmG

mGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NOs: 860); or

LONGEST + GOLD:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAmUmCAAmCmUmUGGACUUCGGUCCmAmAm
GUGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 861);
wherein "mN" indicates a 2′-OMe modification of the nucleotide "N", and "Ns" indicates that the nucleotide "N" is linked to the following nucleotide by a phosphorothioate (PS), more in particular wherein one or more or the one or more guide RNAs are covalently linked at the 5' end to a peptide having the following amino acid sequence: CKRTADGSEFESPKKKRKV (SEQ ID NO: 858), or

(h) the base editor comprises a linker peptide between the deaminase domain and the napDNAbp domain, wherein the linker peptide comprises the amino acid sequence KGPKPKKEESEK (SEQ ID NO: 940); or

(i) the editing rate is greater than 35%, more in particular wherein the editing rate is greater than 50%; or

(j) the one or more guide RNAs comprise a spacer consisting of from about 19 to about 23 nucleotides, more in particular wherein the spacer consists of 21 nucleotides; or

(k) the a lipid nanoparticle comprising the one or more guide RNAs and an mRNA molecule encoding the base editor is to be administered to the subject.

8. The one or more guide RNAs, or one or more polynucleotides encoding the one or more guide RNAs, and the base editor, or one or more polynucleotides encoding the base editor; for the use of claim 6 or claim 7, wherein:

(a) the nucleobase alteration effects an alteration to an encoded amino acid residue, wherein the alteration disrupts opsonization by C3; or

(b) the nucleobase alteration disrupts splicing of a C3 transcript; or

(c) the nucleobase alteration effects an alteration to an encoded amino acid residue, wherein the alteration disrupts cleavage of the C3 polypeptide by a C3 convertase; or

(d) said one or more guide RNAs targets said base editor to effect an alteration of a nucleobase in a start codon of the C3 polynucleotide; or

(e) C3 activity and/or expression is reduced by at least about 50% or 60% as compared to a control subject without the alteration; or

(f) the inappropriate activation of the complement system is associated with increased levels of one or more of inflammation, the presence of autoantibodies, neural degeneration, and microthrombosis; or

(g) the inappropriate activation of the complement system is associated with damage to the central nervous system (CNS), the eyes, the gastrointestinal system, the pulmonary system, the musculoskeletal system, the circulatory system, the integumentary system, blood cells, thyroid, kidney, joints, gastrointestinal system, or transplanted organs; or

(h) the disease or disorder is selected from the group consisting of acute antibody-mediate rejection, age-related macular degeneration, allergic bronchopulmonary aspergillosis, allergic neuritis, allergic rhinitis, amyotrophic lateral sclerosis, anaphylaxis, and scleritis, atopic dermatitis, atypical hemolytic syndrome (aHUS), autoimmune hemolytic anemia, Bechet's disease, bronchiolitis, C3 glomerulopathy, central nervous system (CNS) inflammatory disorders, choroidal neovascularization (CNV), choroiditis, chronic allograft vasculopathy, chronic hepatitis, chronic muscle inflammation, chronic pain, chronic pancreatitis, chronic urticaria, Churg-Strauss syndrome, conjunctivitis, cyclitis, demyelinating disease, dermatitis, dermatomyositis, diabetic retinopathy, encephalitis, eosinophilic pneumonia, geographic atrophy, giant cell arteritis, glaucoma, glomerulonephritis, graft or transplant rejection or failure, HELLP syndrome, Henoch-Schonlein purpura, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis (IPF), IgA nephropathy (IgAN), inflammatory bowel diseases, inflammatory joint conditions, inflammatory skin diseases, infusion reactions, interstitial pneumonia, iridocyclitis, iritis, ischemia/reperfusion injury, Kawasaki disease, keratitis, lupus nephritis, membranoproliferative glomerulonephritis (MPGN), meningitis, microscopic polyangiitis, myasthenia gravis, myocarditis, nasal polyposis, neuromyelitis optica, neuropathic pain, ocular inflammation, osteoarthritis, pancreatitis, panniculitis, paroxysmal nocturnal hemoglobinuria (PNH), pars planitis, pemphigoid, pemphigus, polyarteritis nodosa, polymyositis, primary membranous nephropathy, proliferative vitreoretinopathy, proteinuria, psoriasis, pulmonary fibrosis, renal disease, respiratory distress syndrome, retinal neovascularization (RNV), retinopathy of prematurity, rheumatoid arthritis (RA), rhinosinusitis, sarcoid, sarcoidosis, scleritis, scleroderma, sclerodermatomyositis, sclerosis, Sjögren syndrome, systemic lupus erythematosus, systemic scleroderma, Takayasu's arteritis, thyroiditis, thyroidoisis, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis.

9. Use of one or more guide RNAs, or one or more polynucleotides encoding the one or more guide RNAs in combination with 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) said one or more guide RNAs targets said base editor to effect an alteration of the nucleobase of the C3 polynucleotide that disrupts a splice site in the C3 polynucleotide;
(b) the deaminase domain is a TadA variant (TadA*) comprising a combination of alterations listed in Table 5A, 5B, 5C, 5D, 5E, 6A, 6B, 6C, 6D, 6E, 6F, or 7, wherein the TadA* is not TadA*7.9 or TadA*7.10,
(c) the one or more guide RNAs comprise a nucleic acid sequence comprising at least 10-23 contiguous nucleotides of a spacer nucleic acid sequence listed in any one of Tables 1A, 1B, 1C, 1D, 1E, 1F, and 2; or

(d) said one or more guide RNAs 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 A741, S742, H743, A747, L746, R748, S749, I1125, H1126, Q1127, and E1128 relative to the following reference sequence:

C3 amino acid sequence

MGPTSGPSLLLLLLTHLPLALGSPMYSIITPNILRLESEETMVLEAHDAQGDVPVTVT
VHDFPGKKLVLSSEKTVLTPATNHMGNVTFTIPANREFKSEKGRNKFVTVQATFGTQ
VVEKVVLVSLQSGYLFIQTDKTIYTPGSTVLYRIFTVNHKLLPVGRTVMVNIENPEGIP
VKQDSLSSQNQLGVLPLSWDIPELVNMGQWKIRAYYENSPQQVFSTEFEVKEYVLPS
FEVIVEPTEKFYYIYNEKGLEVTITARFLYGKKVEGTAFVIFGIQDGEQRISLPESLKRI
PIEDGSGEVVLSRKVLLDGVQNPRAEDLVGKSLYVSATVILHSGSDMVQAERSGIPIV
TSPYQIHFTKTPKYFKPGMPFDLMVFVTNPDGSPAYRVPVAVQGEDTVQSLTQGDG
VAKLSINTHPSQKPLSITVRTKKQELSEAEQATRTMQALPYSTVGNSNNYLHLSVLRT
ELRPGETLNVNFLLRMDRAHEAKIRYYTYLIMNKGRLLKAGRQVREPGQDLVVLPL
SITTDFIPSFRLVAYYTLIGASGQREVVADSVWVDVKDSCVGSLVVKSGQSEDRQPV
PGQQMTLKIEGDHGARVVLVAVDKGVFVLNKKNKLTQSKIWDVVEKADIGCTPGS
GKDYAGVFSDAGLTFTSSSGQQTAQRAELQCPQPAARRRRSVQLTEKRMDKVGKYP
KELRKCCEDGMRENPMRFSCQRRTRFISLGEACKKVFLDCCNYITELRRQHARASHL
GLARSNLDEDIIAEENIVSRSEFPESWLWNVEDLKEPPKNGISTKLMNIFLKDSITTWE
ILAVSMSDKKGICVADPFEVTVMQDFFIDLRLPYSVVRNEQVEIRAVLYNYRQNQEL
KVRVELLHNPAFCSLATTKRRHQQTVTIPPKSSLSVPYVIVPLKTGLQEVEVKAAVY
HHFISDGVRKSLKVVPEGIRMNKTVAVRTLDPERLGREGVQKEDIPPADLSDQVPDT
ESETRILLQGTPVAQMTEDAVDAERLKHLIVTPSGCGEQNMIGMTPTVIAVHYLDET
EQWEKFGLEKRQGALELIKKGYTQQLAFRQPSSAFAAFVKRAPSTWLTAYVVKVFS
LAVNLIAIDSQVLCGAVKWLILEKQKPDGVFQEDAPVIHQEMIGGLRNNNEKDMAL
TAFVLISLQEAKDICEEQVNSLPGSITKAGDFLEANYMNLQRSYTVAIAGYALAQMG

RLKGPLLNKFLTTAKDKNRWEDPGKQLYNVEATSYALLALLQLKDFDFVPPVVRW
LNEQRYYGGGYGSTQATFMVFQALAQYQKDAPDHQELNLDVSLQLPSRSSKITHRI
HWESASLLRSEETKENEGFTVTAEGKGQGTLSVVTMYHAKAKDQLTCNKFDLKVTI
KPAPETEKRPQDAKNTMILEICTRYRGDQDATMSILDISMMTGFAPDTDDLKQLANG
VDRYISKYELDKAFSDRNTLIIYLDKVSHSEDDCLAFKVHQYFNVELIQPGAVKVYA
YYNLEESCTRFYHPEKEDGKLNKLCRDELCRCAEENCFIQKSDDKVTLEERLDKACE
PGVDYVYKTRLVKVQLSNDFDEYIMAIEQTIKSGSDEVQVGQQRTFISPIKCREALKL
EEKKHYLMWGLSSDFWGEKPNLSYIIGKDTWVEHWPEEDECQDEENQKQCQDLGA
FTESMVVFGCPN (SEQ ID NO: 796), or a corresponding position in another C3 polypeptide sequence; or

(e) said one or more guide RNAs targets said base editor to effect an alteration of a nucleobase in a start codon of the C3 polynucleotide; or

(f)(1) the deaminase domain is selected from the group consisting of TadA*8.8, TadA*8.13, TadA*8.17, TadA*8.20, TadA*8.8_V82T, TadA*8.8_V82T_Y147T_Q154S, TadA*8.17_V82T, TadA*8.17_V82T_Y147T_Q154S, TadA*8.20_V82T, TadA*8.20_V82T_Y147T_Q154S, rAPOBEC1, and ppAPOBEC; and

(2) the one or more guide RNAs comprise a spacer corresponding to a guide polynucleotide selected from the group consisting of gRNA661, gRNA662, gRNA676, gRNA695, gRNA696, gRNA701, gRNA715, gRNA821, gRNA837, gRNA838, gRNA827, gRNA828, gRNA829, gRNA1793, gRNA1798, gRNA3342, gRNA3343, and gRNA3345; in the preparation of a combination medicament for treating acute antibody-mediate rejection, age-related macular degeneration, allergic bronchopulmonary aspergillosis, allergic neuritis, allergic rhinitis, amyotrophic lateral sclerosis, anaphylaxis, and scleritis, atopic dermatitis, atypical hemolytic syndrome (aHUS), autoimmune hemolytic anemia, Bechet's disease, bronchiolitis, C3 glomerulopathy, central nervous system (CNS) inflammatory disorders, choroidal neovascularization (CNV), choroiditis, chronic allograft vasculopathy, chronic hepatitis, chronic muscle inflammation, chronic pain, chronic pancreatitis, chronic urticaria, Churg-Strauss syndrome, conjunctivitis, cyclitis, demyelinating disease, dermatitis, dermatomyositis, diabetic retinopathy, encephalitis, eosinophilic pneumonia, geographic atrophy, giant cell arteritis, glaucoma, glomerulonephritis, graft or transplant rejection or failure, HELLP syndrome, Henoch-Schonlein purpura, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis (IPF), IgA nephropathy (IgAN), inflammatory bowel diseases, inflammatory joint conditions, inflammatory skin diseases, infusion reactions, interstitial pneumonia, iridocyclitis, iritis, ischemia/reperfusion injury, Kawasaki disease, keratitis, lupus

nephritis, membranoproliferative glomerulonephritis (MPGN), meningitis, microscopic polyangiitis, myasthenia gravis, myocarditis, nasal polyposis, neuromyelitis optica, neuropathic pain, ocular inflammation, osteoarthritis, pancreatitis, panniculitis, paroxysmal nocturnal hemoglobinuria (PNH), pars planitis, pemphigoid, pemphigus, polyarteritis nodosa, polymyositis, primary membranous nephropathy, proliferative vitreoretinopathy, proteinuria, psoriasis, pulmonary fibrosis, renal disease, respiratory distress syndrome, retinal neovascularization (RNV), retinopathy of prematurity, rheumatoid arthritis (RA), rhinosinusitis, sarcoid, sarcoidosis, scleritis, scleroderma, sclerodermatomyositis, sclerosis, Sjögren syndrome, systemic lupus erythematosus, systemic scleroderma, Takayasu's arteritis, thyroiditis, thyroidoisis, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis

10. The one or more guide RNAs, or one or more polynucleotides encoding the one or more guide RNAs, and the base editor, or one or more polynucleotides encoding the base editor; for the use of claim 6 or claim 7, wherein:

(a) the one or more guide RNAs, or one or more polynucleotides encoding the one or more guide RNAs, and a base editor is to be administered locally; or

(b) the C3 polynucleotide is to be contacted with two or more guide RNAs, and wherein each guide RNA binds a different location within the C3 polynucleotide; or

(c) the nucleobase alteration results in a premature STOP codon or

(d) the subject is a mammal; or

(e) wherein the one or more guide RNAs, or one or more polynucleotides encoding the one or more guide RNAs, and the base editor, or one or more polynucleotides encoding the base editor, is to be administered a second timeabout or at least about 1 month, 6 months, or a year after a first administration.

[JYC1]

11. A base editor system comprising 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, and one or more guide polynucleotides, or one or more polynucleotides encoding the one or more guide polynucleotides, wherein the one or more guide polynucleotides comprise at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleobases of a spacer listed in **Table 1A, 1B, 1C, 1D, 1E, 1F, or 2**.

12. The base editor system of claim 11, wherein:

(a) the deaminase is a deaminase selected from the group consisting of TadA*8.8, TadA*8.13, TadA*8.17, TadA*8.20, TadA*8.8_V82T, TadA*8.8_V82T_Y147T_Q154S, TadA*8.17_V82T, TadA*8.17_V82T_Y147T_Q154S, TadA*8.20_V82T, and TadA*8.20_V82T_Y147T_Q154S, rAPOBEC1, and ppAPOBEC; or

(b) the base editor is selected from the group consisting of ABE8.8, ABE8.13, ABE8.17, ABE8.20, ABE8.8_V82T, ABE8.8_V82T_Y147T_Q154S, ABE8.17_V82T, ABE8.17_V82T_Y147T_Q154S, ABE8.20_V82T, ABE8.20_V82T_Y147T_Q154S, BE4, and those base editors listed in **Tables 1A, 1B, 1C, 1D, 1E, 1F, 2, and 8-15**; or

(c) the guide polynucleotide comprises a spacer consisting of from about 19 to about 23 nucleotides, in particular wherein the spacer consists of 21 nucleotides; or

(d) the one or more guide polynucleotides comprise a spacer corresponding to a guide polynucleotide selected from the group consisting of gRNA676, gRNA661, gRNA715, gRNA821, gRNA837, gRNA838, gRNA827, gRNA828, gRNA829, gRNA3342, gRNA3343, and gRNA3345; or

(e) the napDNAbp domain comprises a Cas9 variant, in particular wherein the Cas9 variant comprises one or more of the amino acid alterations A1283D and E1250K relative to an SpCas9 reference amino acid sequence; or wherein the Cas9 variant comprises one or more of the following combinations of amino acid alterations relative to an spCas9 reference amino acid sequence:
I322V, S409I, E427G, R654L, R753G, and R1114G;
I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, and R1337K;
I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, R1337K, and A1283D;
I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, R1337K, A1283D, R220A, and R221A;
I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, R1337K, A1283D, R765A, and Q768A;
I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, Q1136Y, R1337K, A1283D, R765A, Q768A, K772A, and K775A;
I322V, S409I, E427G, R654L, R753G, R1114G, M1135L, R1337K, A1283D, and E1250K;
I322V, S409I, E427G, R654L, R753G, R1114G, Q1136Y, A1283D, and E1250K;

I322V, S409I, E427G, R654L, R753G, R1114G, Q1136Y, and R1337K; and
I322V, S409I, E427G, R654L, R753G, R1114G, and R1337K; or
h wherein the Cas9 variant is SaCas9-KHH, SpCas9-MQKFRAER, or SpCas9-VRQR; or

(f) the base editor comprises a linker between the deaminase domain and the napDNAbp domain, wherein the linker comprises the amino acid sequence KGPKPKKEESEK (SEQ ID NO: 940).

13. The base editor system of claim 11, wherein the one or more guide polynucleotides comprise a nucleic acid analog, in particular wherein the one or more guide polynucleotides comprise one or more of a 2′-OMe and a phosphorothioate, more in particular wherein the one or more guide polynucleotides comprise one of the following nucleotide sequences:
End-mod SpCas9 guide polynucleotide:
mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO: 943);
End-mod SaCas9 guide polynucleotide:
mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGUACUCUGUAAUGAAAAUUACAGAAUCUA
CUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU
(SEQ ID NO: 944);
HM01:
mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGU
UAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmG
mAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 855);
HM07:
mNsmNsmNsmNmNmNmNmNmNmNNNNNNNNNNNNmGUUUUAGmAmGmCmUmAmGmAmAmAmUm
AmGmCmAmAGUUmAAmAAmUAmAmGmGmCmUmAGUmCmCGUUAmUmCAAmCmUmUmGmAmAm
AmAmAmGmUmGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 856);
NLS (bpsv40):
mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU (SEQ ID NOs: 857);

LONGEST:
mNsmNsmNsNNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGUGmG
mCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 859);
NLS + LONGEST :
mNsmNsmNsNNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmG
mGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NOs: 860); or
LONGEST + GOLD:
mNsmNsmNsNNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAmUmCAAmCmUmUGGACUUCGGUCCmAmAm
GUGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 861);
wherein "mN" indicates a 2′-OMe modification of the nucleotide "N", and "Ns" indicates that the nucleotide "N" is linked to the following nucleotide by a phosphorothioate (PS), more in particular wherein the one or more guide polynucleotides comprise a scaffold covalently linked at the 5' end to a peptide having the following amino acid sequence: CKRTADGSEFESPKKKRKV (SEQ ID NO: 858).

14. A polynucleotide or set of polynucleotides encoding the base editor system of any one of claims 11-13, or a component thereof.

15. A kit comprising the base editor system of any one of claims 11-14 for the use as defined in any one of claims 1-8 and 10.

16. A pharmaceutical composition comprising an effective amount of the base editor system of any one of claims 11-13.

17. A guide polynucleotide comprising a spacer sequence listed in **Table 1A, 1B, 1C, 1D, 1E, 1F, or 2**.

18. A base editor system comprising 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, and one or more guide polynucleotides, or one or more polynucleotides encoding the one or more guide polynucleotides, wherein

a) the guide polynucleotide comprises a spacer corresponding to gRNA676, the napDNAbp domain is an SpCas9, and the deaminase domain is selected from the group consisting of TadA*8.8 with the amino acid alterations V82T, Y147T, and Q154S, TadA*8.20 with the amino acid alterations V82T, Y147T, and Q154S, TadA*8.8, TadA*8.13, and TadA*8.20 with the amino acid alteration V82T;

b) the guide polynucleotide comprises a spacer corresponding to gRNA661, the napDNAbp domain is an SpCas9 or an SpCas9 with the amino acid alterations A1283D and E1250K, and the deaminase domain is selected from the group consisting of TadA*8.20 with the amino acid alterations V82T, Y147T, and Q154S, TadA*8.8, TadA*8.13, TadA*8.20, TadA*8.8 with the amino acid alteration V82T, TadA*8.8 with the amino acid alterations V82T, Y147T, and Q154S, and TadA*8.20 with the amino acid alteration V82T;

c) the guide polynucleotide comprises a spacer corresponding to gRNA696, the napDNAbp domain is an SpCas9 or an SpCas9 with the amino acid alterations A1283D and E1250K, and the deaminase domain is selected from the group consisting of TadA*8.8, TadA*8.13, TadA*8.20, TadA*8.20 with the amino acid alteration V82T, and TadA*8.20 with the amino acid alterations V82T, Y147T, and Q154S;

d) the guide polynucleotide comprises a spacer corresponding to gRNA715, the napDNAbp domain is an SpCas9 or an SpCas9-VRQR, and the deaminase domain is selected from the group consisting of TadA*8.8, TadA*8.13, and TadA*8.20 with the amino acid alteration V82T;

e) the guide polynucleotide comprises a spacer corresponding to gRNA821, the napDNAbp is an SpCas9, the deaminase domain is a cytidine deaminase domain, and the base editor further comprises two uracil glycosylase inhibitors;

f) the guide polynucleotide comprises a spacer corresponding to gRNA827 , the napDNAbp is an SpCas9, and the deaminase domain is TadA*8.8;

g) the guide polynucleotide comprises a spacer corresponding to gRNA828 , the napDNAbp is h) an SpCas9, and the deaminase domain is TadA*8.8;

h) the guide polynucleotide comprises a spacer corresponding to gRNA829, the napDNAbp is an SpCas9, and the deaminase domain is TadA*8.8;

i) the guide polynucleotide comprises a spacer corresponding to gRNA837, the napDNAbp is an SpCas9-VRQR, and the deaminase domain is TadA*8.8;

j) the guide polynucleotide comprises a spacer corresponding to gRNA838, the napDNAbp is an SpCas9-VRQR, and the deaminase domain is TadA*8.8;

k) the guide polynucleotide comprises a spacer corresponding to gRNA3342, the napDNAbp is an SpCas9, and the deaminase is selected from the group consisting of TadA*8.8, TadA*8.13, TadA*8.20, TadA*8.8 with the amino acid alterations V82T, Y147T, and Q154S, TadA*8.17 with the amino acid alteration V82T, TadA*8.17 with the amino acid alterations V82T, Y147T, and Q154S, TadA*8.20 with the amino acid alteration V82T, and TadA*8.20 with the amino acid alterations V82T, Y147T, and Q154S;

l) the guide polynucleotide comprises a spacer corresponding to gRNA3343, the napDNAbp is selected from the group consisting of

i) SpCas9-MQKFRAER;

ii) SpCas9-MQKFRAER with the combination of amino acid alterations I322V, S409I, E427G, R654L, R753G, R1114G, and R1337K;

iii) SpCas9-MQKFRAER with the combination of amino acid alterations I322V, S409I, E427G, R654L, R753G, R1114G, Q1136Y, A1283D, and E1250K; and

iv) SpCas9-MQKFRAER with the combination of amino acid alterations I322V, S409I, E427G, R654L, R753G, and R1114G; and

the deaminase domain is TadA*8.20 or TadA*7.10; or

m) the guide polynucleotide comprises a spacer corresponding to gRNA3345, the napDNAbp domain is an SaCas9-KHH, the deaminase domain is a cytidine deaminase domain, and the base editor further comprises two uracil glycosylase inhibitors.

19. The base editor system of claim 18, wherein:

(a) the napDNAbp domain is a nickase; or

(b) the deaminase domain and the napDNAbp domain are separated by a linker comprising the amino acid sequence KGPKPKKEESEK (SEQ ID NO: 940); or

. (c) the polynucleotide encoding the base editor is codon optimized; or

(d) the one or more guide polynucleotides comprises a sequence selected from the group consisting of:

HM07:

mNsmNsmNsmNmNmNmNmNmNmNNNNNNNNNNNNmGUUUUAGmAmGmCmUmAmGmAmAmAmUm

AmGmCmAmAGUUmAAmAAmUAmAmGmGmCmUmAGUmCmCGUUAmUmCAAmCmUmUmGmAmAm
AmAmAmGmUmGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO:
856);

End-mod SpCas9 guide polynucleotide:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO:
943);

End-mod SaCas9 guide polynucleotide:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGUACUCUGUAAUGAAAAUUACAGAAUCUA
CUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU
(SEQ ID NO: 944);

HM01:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGU
UAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmG
mAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 855);

NLS (bpsv40):

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU (SEQ ID NOs:
857);

LONGEST:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGUGmG
mCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 859);

NLS + LONGEST :

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmG
mGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NOs: 860); and

LONGEST + GOLD:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAmUmCAAmCmUmUGGACUUCGGUCCmAmAm
GUGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 861);

wherein “mN” indicates a 2′-OMe modification of the nucleotide “N”, and “Ns” indicates that the nucleotide “N” is linked to the following nucleotide by a phosphorothioate (PS), in

particular wherein the one or more guide polynucleotides comprise a scaffold covalently linked at the 5' end to a peptide having the following amino acid sequence: CKRTADGSEFESPKKKRKV (SEQ ID NO: 858); or

(e) the one or more guide polynucleotides are selected from the group consisting of gRNA661, gRNA676, gRNA2203, gRNA4232.

20. A polynucleotide or set of polynucleotides encoding the base editor system of claim 17.

21. A cell or lipid nanoparticle comprising the base editor system of claim 18.

22. An *in vitro* or *ex vivo* method for altering a nucleobase of a complement component 3 (C3) polynucleotide, the method comprising contacting the C3 polynucleotide with the base editor system of claim 18.

23. The base editor of claim 18 for use in treating a disease or disorder associated with inappropriate activation of the complement system in a subject in need thereof, wherein the base editor system is to be administered to the subject.